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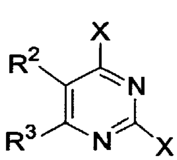
(54) **Title:** 2- AND 4-AMINOPYRIMIDINES N-SUBSTTITUDED BY A BICYCLIC RING FOR USE AS KINASE INHIBITORS IN THE TREATMENT OF CANCER



(I)

(57) **Abstract:** A coumpound of the formula (I) wherein each X is independently NR^1R^6, NR^4R^5, or R^4, with the proviso that at least one X must be NR^1R^6; each R^1 is independently an optionally substituted fused bicyclic unsaturated ring containing 9 or 10 atoms optionally containing 1-4 heteroatoms selected from the group consisting of N, S and O, and the variables R^{2-6} are as defined in claim 1, are claimed. These compounds are kinase inhibitors useful in the treatment of cancer and viral infections.

WO 03/030909 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

2- AND 4-AMINOPYRIMIDINES N-SUBSTITUTED BY A BICYCLIC RING FOR USE AS KINASE INHIBITORS IN THE TREATMENT OF CANCER

BACKGROUND

Technical Field

The present invention relates to certain multi-ring compounds, particularly to compounds that are useful as inhibitors of kinases such as, but not limited to, serine/threonine kinases. The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention, as well as methods of using the compounds in inhibiting the kinases and treating patients suffering from diseases caused by various altered kinases. The invention also relates to a method of producing the compounds of the present invention. In addition, the present invention relates to intermediates used to prepare the compounds of the present invention.

Background of the Invention

At the present time, many cancer treatments use components that interfere with cell division by unspecific mechanisms such as inhibition of DNA synthesis. Although toxic in general, these compounds have a toxic effect on the rapidly growing tumor cells that can provide an effective cancer treatment. However, anti-cancer compounds that act by mechanisms more specific to cancer cells rather than inhibiting DNA synthesis have the potential to display enhanced specificity to cancer cells.

For example, serine/threonine protein kinases are involved in cellular signaling mechanisms that regulate gene expression and cell proliferation (Su and Karin, Curr. Opinion. Immunol. (1996), 8:402; Kolch, Biochem. J. (2000) 351:289). Some serine/threonine kinases, such as cyclin dependent kinases (CDK), are necessary to progress from one step in the cell cycle to the next (Meyerson et al., EMBO J. (1992) 11:2909). They are active when specifically bound to other cell cycle proteins (cyclin family). Changes in their activities or in the activities of their activators or inhibitors are common in cancerous cells (Motokura and Arnold,

Biochim. Biophys. Acta (1993) 1155:63). The frequent deregulation of kinase activities in cancer and the discovery of natural inhibitors of cyclin dependent kinases have stimulated the active search for chemical inhibitors of CDK proteins (Vesely et al., Eur. J. Biochem. (1994) 224771).

Apoptosis, the programmed cell death, plays an important role in the embryogenesis, regulation of the immune cell populations and probably aging. Failures in apoptotic signal transduction pathways lead to a variety of diseases including tumors (Hug, Biol. Chem. (1997) 378:1412). It is widely recognized that the induction of apoptosis holds promise as a treatment strategy for cancer. In fact, a number of chemotherapeutic agents have already been identified that induce apoptosis in cancer cells in vitro (Arends and Wyllie, Int. Rev. Exp. Pathol. (1991) 32:223 and Mesner et al., Adv. Pharmacol. (1997) 41:461).

Apoptosis is an intrinsic process present in all cells that can be regulated by extrinsic factors such as hormones, growth factors, cell surface receptors or cellular stress. The actions of both pro- and anti-apoptotic factors are often affected by modulation of the phosphorylation state of key elements of the apoptotic process. Evidence has been accumulated that serine/threonine kinases are also involved directly in the regulation of the apoptotic cascade (Cross et al., Experimental Cell Research (2000) 256:34). Because apoptosis is regulated, biochemical alterations that make cells more or less susceptible to apoptosis might affect their sensitivity to a broad range of anti-neoplastic agents (Kaufmann and Earnshaw, Experimental Cell Research (2000) 256:42). Therefore, new drugs that sensitize tumor cells for apoptosis or induce apoptosis by interfering with key regulators of the apoptotic process such as serine/threonine kinases would be of great benefit for future cancer treatment strategies.

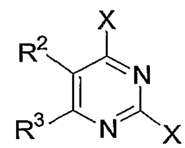
Viruses are by definition unable to replicate on their own but must enter a host cell in order to use the host cell's macromolecular machinery to replicate (Knipe in: Fields et al., <u>Virology, Third Edition</u> (Lippincott-Raven, 1996), p. 273. Inhibition of protein kinases has also shown encouraging results in controlling viral infections such as infections with human cytomegaloviruses (Bresnahan et al., Virology (1997) 231:239).

Therefore, controlled inhibition of serine-threonine kinase activities are useful in controlling and treating diseases such as cancer and viral infections.

Accordingly, it is desirable to develop inhibitors of kinases including serine/threonine kinases.

SUMMARY OF THE INVENTION

The present invention relates to certain multi-ring compounds represented by the Formula (I):



(I)

wherein

each X is independently NR^1R^6, NR^4R^5, or R^4, with the proviso that at least one X must be NR^1R^6;

each R^1 is independently an optionally substituted fused bicyclic unsaturated ring containing 9 or 10 atoms and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein said substitution on said ring is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, optionally substituted alkyl, and optionally substituted alkenyl wherein the substitution on said alkyl and alkenyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl;

R^2 is hydrogen, halo, optionally substituted alkyl, or an optionally substituted $-Y_{(n)}$-mono-ring group or $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, $-OR^8$, -C=O, $-NO_2$, $-CONR^8R^9$, and optionally substituted alkyl, wherein said substitution on each of said alkyls is independently selected from the group consisting of $-NR^8R^9$, $-OR^8$, and fluoro;

R^3 is hydrogen, alkyl, or halo;

each R^4 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight- or branched-chain C_2-C_3-alkylenyl and -C(CN)-; wherein R^4 can also be hydrogen or alkyl when R^5 is present; and wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl, wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^5 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or an optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and $-N=CHCH_3$; and wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^6 is independently hydrogen or alkyl;

each R^8 and R^9 is independently hydrogen, optionally substituted C_{1-5}-alkyl, optionally substituted aryl, or optionally substituted arylalkyl, wherein said substitution is selected from the group consisting of

optionally substituted alkyl, wherein said substitution on said alkyl is selected from the group consisting of fluoro and dialkylamino;

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to compounds of Formula (I) wherein:

each X individually is $-NR^1R^6$, $-NR^4R^5$, or R^4, with the proviso that at least one X is $-NR^1R^6$;

each R^1 is independently an optionally substituted moiety selected from the group consisting of indazolyl, quinolinyl, benzothiazolyl, benzotriazolyl, or benzoxazolyl, wherein said substitution is selected from the group consisting of hydrogen, methyl, and ethyl;

R^2 is halo or optionally substituted alkyl, wherein said substitution is selected from the group consisting of fluoro, $-COOR^8$, $-COOR^9$, and $-CONR^8R^9$;

R^3 is hydrogen or methyl;

each R^4 is hydrogen, methyl, phenyl, aryl, benzothiophenyl, pyridyl, indolyl, naphthalenyl, biphenyl, indanyl, indenyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzotriazolyl, cyclohexanyl, cyclopentanyl, cyclobutanyl, or multiple rings which are linked covalently, either directly or via a linker, wherein said linker is selected from the group consisting of methylene, O, S, N, $-R^8-SO_2$, $-SO_2-NR^8$, $-NR^8CO-$ and $-CONR^8$;

each R^5 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or an optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and $-N=CHCH_3$; and wherein said substitution is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl, wherein said substitution on said alkyl is

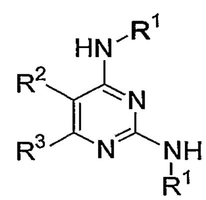
selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^6 is independently hydrogen or alkyl;

each R^8 and R^9 is independently hydrogen, optionally substituted C_{1-5}-alkyl, optionally substituted aryl, and optionally substituted arylalkyl, wherein said substitution is selected from the group consisting of optionally substituted alkyl; wherein said substitution on said alkyl is selected from the group consisting of fluoro and dialkylamino;

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to compounds of Formula (I-1)



(I-1)

wherein

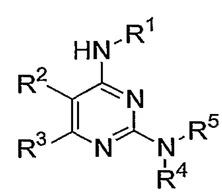
each R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, bromo, chloro, methyl, or trifluoromethyl; and

R^3 is hydrogen or methyl,

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to compounds of Formula (I-2)



(I-2)

wherein:

each R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, bromo, chloro, methyl, or trifluoromethyl;

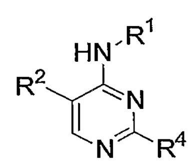
R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl; and

R^5 is an optionally substituted moiety selected from the group consisting of phenyl, pyridyl, thiophene, furan, $-Y_{(n)}$-mono-ring group or $-Y_{(n)}$-multi-ring group, said ring group in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight or branched-chain C_{2-3}-alkenyl, -N=CH, and $-N=CHCH_3$; and wherein said substitution is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to compounds of Formula (I-3)



(I-3)

wherein:

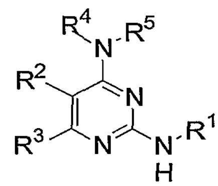
R^1 is 5-quinolyl or 6-quinolyl;

R^2 is fluoro or trifluoromethyl; and

R^4 is optionally substituted phenyl or pyridyl, wherein said substitution is selected from the group consisting of halo, amino, hydroxy, acetyl, alkyl, alkoxy, alkenyl, hydroxyalkyl, dialkylamino, and phenyl;

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to the compounds of Formula (I-4)



(I-4)

wherein:

R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, chloro, bromo, methyl, or trifluoromethyl;

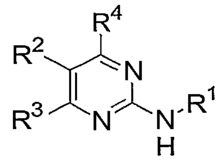
R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl; and

R^5 is an optionally substituted -Y(n)-moiety, wherein n is 0 or 1, Y is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and -N-$CHCH_3$, and said moiety is selected from the group consisting of cycloalkyl, phenyl, naphthyl, pyridyl, thienyl, furyl, quinolinyl, benzothiophenyl, benzothiazolyl, indol-3-yl, and quinoline-4-thio, said substitution being selected from the group consisting of methyl, ethyl, fluoro, bromo, chloro, trifluoromethyl, methoxyl, methylenedioxyl, sulfonamidyl, morpholinyl, and -pyrazinyl; and

and pharmaceutically acceptable salts and prodrugs thereof.

The present invention also relates to compounds of Formula (I-5)



(I-5)

wherein:

R^1 is 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, methyl, bromo, chloro, trifluoromethyl, $-CO_2CH_3$, $-CO_2H$, and -CO-morpholinyl;

R^3 is hydrogen or methyl; and

R^4 is an optionally substituted $-Y_{(n)}$-mono-ring group or optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n = 0 or 1, -Y- is -C(CN)-; and wherein said ring group is selected from the group consisting of optionally substituted phenyl or pyridyl, wherein said substitution on said rings is selected from the group consisting of halo, amino, hydroxy, acetyl, alkyl, alkoxy, alkenyl, hydroxyalkyl, dialkylamino, and phenyl;

and pharmaceutically acceptable salts and prodrugs thereof.

Another aspect of the present invention relates to pharmaceutical composition containing at least one of the compounds of the present invention.

The present invention also relates to a method for inhibiting kinases such as serine/threonine kinases in a warm-blooded animal in need thereof by administering at least one of the compounds of the present invention in an amount sufficient to inhibit said kinases.

The present invention also relates to a method for treating a CDK-dependent disorder or disease in a warm-blooded animal in need of same, by administering to said animal at least one of the compounds of the present invention in an amount sufficient to inhibit CDK.

The present invention further relates to a method for inhibiting cellular proliferation in a warm-blooded animal in need thereof by administering to said animal at least one of the compounds of the present invention in an amount sufficient to inhibit said proliferation.

The present invention also relates to methods of treating a warm-blooded animal suffering from cancer or neoplastic disease by administering to said warm-blooded animal an effective amount of at least one of the compounds of the present invention.

A still further aspect of the present invention relates to a method for modulating apoptosis in a warm-blooded animal in need thereof by administering at least one of the compounds of the present invention in an amount sufficient to modulate apoptosis.

In addition, the present invention relates to intermediates used to prepare the above compounds of the present invention.

Still other objects and advantages of the present invention will become readily apparent by those skilled in the art from the following detailed description, wherein are shown and described preferred embodiments of the invention, simply by way of illustration of the best mode contemplated of carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, without departing from the invention. Accordingly, the description is to be regarded as illustrative in nature and not as restrictive.

DETAILED DESCRIPTION OF THE INVENTION

Except as expressly stated otherwise, the term “alkyl”, when used alone or as part of another term, refers to straight- or branched-chain optionally substituted hydrocarbon groups containing 1 to 6 carbon atoms; or optionally substituted cycloalkyl groups. Examples of suitable straight-chain alkyl groups include methyl, ethyl and propyl. Examples of branched-chain alkyl groups include isopropyl and t-butyl. The preferred alkyl group is methyl. The cycloalkyl groups typically contain 3-6 atoms in the ring and can include up to 2 heteroatoms such as N, S and O, and can include unsaturation in the ring. Typical cycloalkyl groups and cycloalkyl groups containing hetero atoms in the ring include cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, 2-pyrrolinyl, imidazolidinyl, 2-imidazolinyl, pyrazolidinyl, 3-pyrazolyl, piperidinyl, piperazinyl and morpholinyl.

The term "alkenyl" refers to straight- or branched-chain optionally substituted hydrocarbon groups containing 2 to 6 carbon atoms comprising one carbon-carbon double bond. Examples of suitable alkenyl groups are methenyl and ethenyl.

The term "alkoxy" refers to straight- or branched-chain optionally substituted C_1-C_6-alkyl-O-, wherein "alkyl" is as defined above.

The term "dialkylamino" refers to a nitrogen atom substituted with two alkyl groups, each alkyl being independently as defined above.

Substitutions for each of the alkyl, alkenyl, alkoxy, and dialkylamino groups are selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitutions on said alkyl are selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl. Examples of suitable halo groups are chloro, bromo and fluoro. An example of a fluoro substituted alkyl is trifluoromethyl. Preferably at least one of R^2 or R^3 is alkyl substituted with either halo or halo-substituted alkyl, and most preferably one of R^5 or R^3 is alkyl substituted with either halo or halo-substituted alkyl and the other of R^5 or R^6 is hydrogen.

The term "hydroxyalkyl" refers to an alkyl as defined above substituted with at least one hydroxy group.

Examples of fused bicyclic unsaturated ring groups are 2-quinolinyl, 3-quinolinyl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 3-cinnolyl, 6-cinnolyl, 7-cinnolyl, 2-quinazolinyl, 4-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl, 1-phthalazinyl, 6-phthalazinyl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-7-yl, 1,7-naphthyridin-3-yl, 1,7-naphthyridin-6-yl, 1,8-naphthyridin-3-yl, 2,6-naphthyridin-6-yl, 2,7-naphthyridin-3-yl, indolyl, 1*H*-indazolyl, benzothiazolyl, benzotriazolyl, purinyl and pteridinyl. Substitutions for each of the fused ring groups are selected from the group consisting of $-NR^8R^9$, $-OR_8$, fluoro, methenyl and ethenyl.

Examples of mono- and multi-ring groups include aryl and bicyclic fused aryl-cycloalkyl groups. The aryl groups include an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently, directly or via a linker, e.g. methylene, O, S, N, $-NR^8SO_2-$, $-COR^8$, $-NR^8CO-$, and $-SO_2-NR^8$. The rings may each contain from zero to four heteroatoms selected from N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl and 6-quinolyl. Substitutions for each of the above noted aryl systems include halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N{=}CR^8$, and optionally substituted alkyl wherein said substitutions on said alkyl are selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl.

The "bicyclic fused aryl-cycloalkyl" groups are those groups in which an aryl ring (or rings) is fused to a cycloalkyl group (including cycloheteroalkyl groups). The group can be attached to the remainder of the molecule through either an available valence on the aryl portion of the group, or an available valence on the cycloalkyl portion of the group. Examples of such bicyclic fused aryl-cycloalkyl groups are indanyl, benzotetrahydrofuranyl, benzotetrahydropyranyl and 1,2,3,4-tetrahydronaphthyl. Substitutions for each of the above noted groups include halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N{=}CR^8$, and optionally substituted alkyl wherein said substitutions on said alkyl are selected from the group consisting of $-NR^8R^9$, OR^8, fluoro, methenyl, and ethenyl.

When a substituted moiety is employed, it can be substituted at one or more positions with at least one of the above disclosed groups up to the number

of available positions, but typically contain 1-3 substitutions, when substituted. When more than one substitution is present, the same or different substitution groups can be employed.

Pharmaceutically acceptable salts of the compounds of the above formulae include those derived from pharmaceutically acceptable, inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, trifluoroacetic and benzenesulfonic acids.

Salts derived from appropriate bases include alkali such as sodium and ammonia or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolyzable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}-alkoxymethyl esters, for example methoxymethyl; C_{1-6}-alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; C_{3-8}-cycloalkoxycarbonyloxy, C_{1-6}-alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}-alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolyzable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-

methoxy. A selection of *in vivo* hydrolyzable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4-position of the benzoyl ring.

Some compounds of the formula (I) may have chiral centers and/or geometric isomeric centers (E- and Z-isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess cyclin-dependent kinase (CDK) inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

The compounds of the present invention can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, e.g. intravenously, subcutaneously, intramuscularly, intraperitoneally, and locally (intratumorally) in sterile liquid dosage forms. The active ingredient can also be administered intranasally (nose drops) or by inhalation of drug powder mist. Other dosage forms are potentially possible such as administration transdermally, via patch mechanism or ointment.

Formulations suitable for oral administration can comprise of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents,

such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, propylene glycol, glycerin, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard-or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of the following: lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, and gels containing, in addition to the active ingredient, such carriers as are known in the art.

Immediate release tablets/capsules solid oral dosage forms are made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, and nitrogen.

They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

Moreover, the compounds of the present invention can be administered in the form of nose drops, or metered dose and a nasal or buccal inhaler. The drug is delivered from a nasal solution as a fine mist or from a powder as an aerosol. The foregoing description of the invention illustrates and describes the present invention.

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol such as poly (ethyleneglycol) 400, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, an oil, a fatty acid, a fatty acid ester or glyceride, or any acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulos, or emulsifying agents and other pharmaceutical adjuvants.

Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isosteric acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include: (a) cationic detergents such as, dimethyldialkylammonium halides, and alkylpyridinium halides, (b) anionic detergents such as, alkyl, aryl, and olefin sulfonates, alkyl, olefin, either, and monoglyceride sulfates, and sulfosuccinates,

(c) nonionic detergents such as, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene polypropylene copolymers, (d) amphoteric detergents such as, alkyl β-aminopropionates, and 2-alkylimidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral formulations typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5% to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

Formulations suitable for topical administration include lozenges comprising the active ingredient in a flavor, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier; as well as creams, emulsions, and gels containing, in addition to the active ingredient, such carriers as are known in the art.

Additionally, formulations suitable for rectal administration may be presented as suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well-known to those who are skilled in the art. Typically, the pharmaceutically acceptable carrier is chemically inert to the active compounds and has no detrimental side effects or toxicity under the conditions of use. The pharmaceutically acceptable carriers can include polymers and polymer matrices.

Pharmaceutically acceptable excipients are also well-known to those who are skilled in the art. The choice of excipient will be determined in part by the particular compound, as well as the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following methods and excipients are merely exemplary and are in no way limiting. The pharmaceutically acceptable excipients preferably do not interfere with the action of the active ingredients and do not cause adverse side-effects. Suitable carriers and excipients include solvents such as water, alcohol, and propylene glycol, solid absorbants and diluents, surface active agents, suspending agent, tableting binders, lubricants, flavors, and coloring agents.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field, incorporated by reference.

The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. *See Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Co., Philadelphia, PA, Banker and Chalmers, Eds., 238-250 (1982) and *ASHP Handbook on Injectable Drugs,* Toissel, 4th ed., 622-630 (1986).

The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the animal over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including a condition of the animal, the body weight of the animal, as well as the severity and stage of the cancer.

A suitable dose is that which will result in a concentration of the active agent in a patient which is known to effect the desired response. The preferred dosage is the amount which results in maximum inhibition of cancer, without unmanageable side effects. The dosage administered will, of course, vary

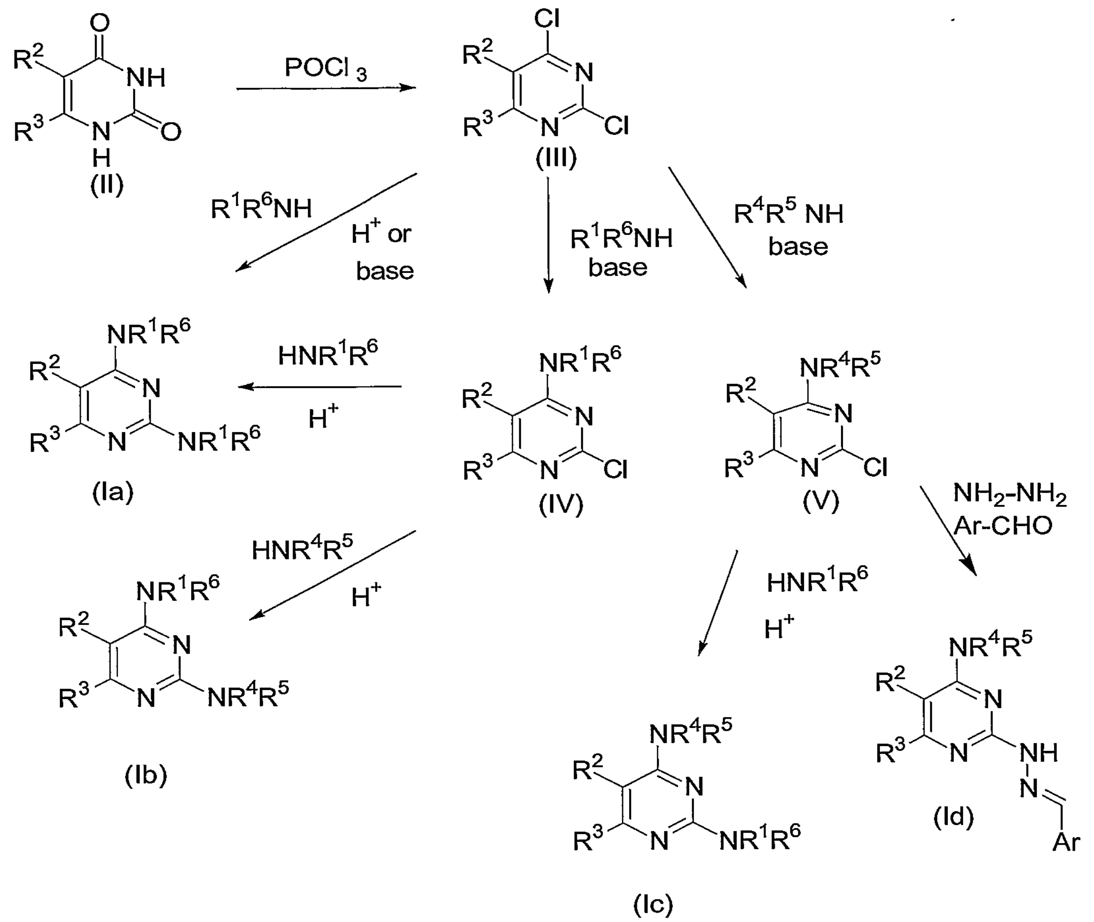
depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. The size of the dose also will be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of the compound and the desired physiological effect. A daily dosage of active ingredient can be expected to be about 0.001 to 1000 milligrams (mg) per kilogram (kg) of body weight, with the preferred dose being 0.1 to about 30 mg/kg.

Dosage forms (compositions suitable for administration) contain from about 1 mg to about 500 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in any amount of about 0.5-95% weight based on the total weight of the composition.

General Preparative Methods

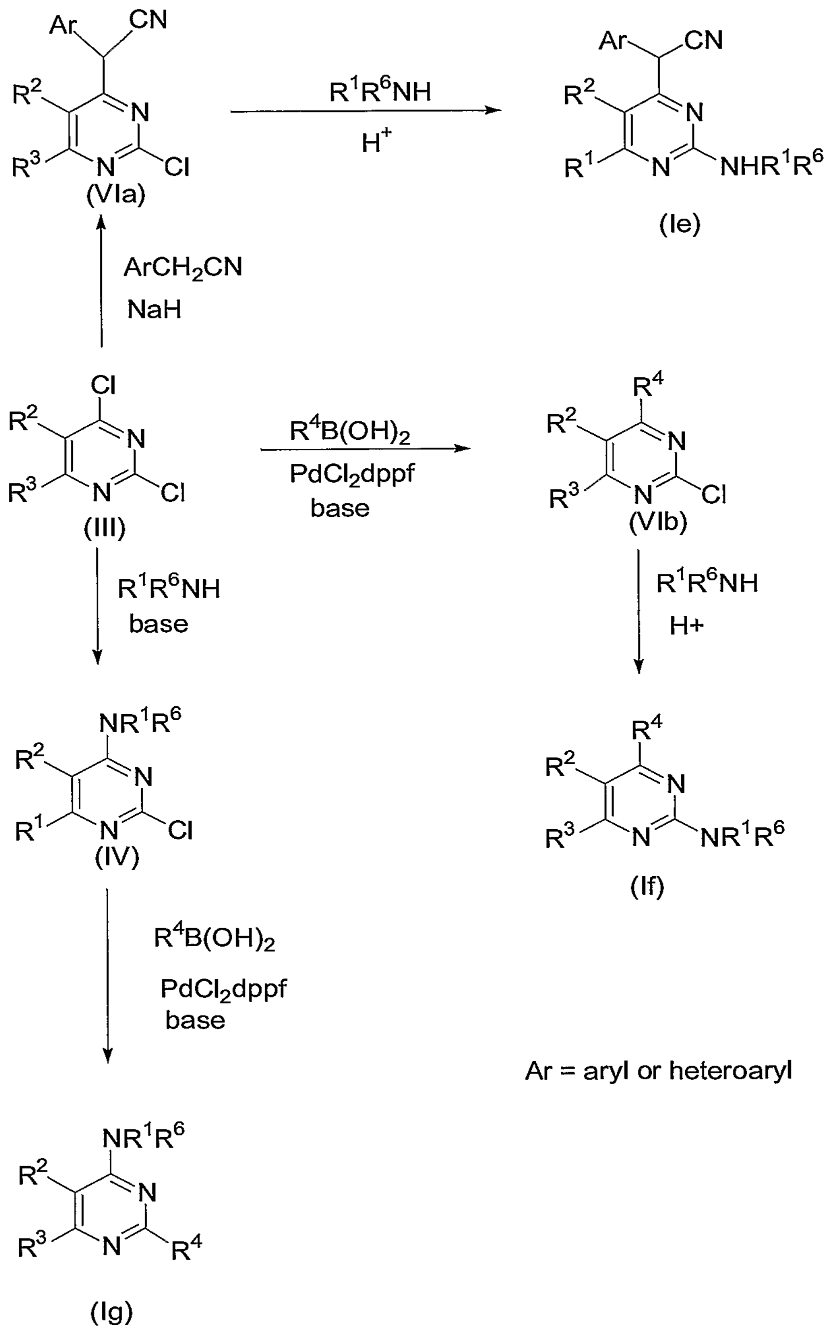
Compounds of formula (I) may be prepared as illustrated in the General Reaction Schemes shown below. In the structures shown below, R^1, R^2, R^3, R^4, R^5, and R^6 are independently selected and have the definitions as described above.

Reaction Scheme 1



Specifically, a 5,6-disubstituted uracil (II) may be converted to a 2,4-dichloro-5,6-disubstituted pyrimidine intermediate of formula (III). This key intermediate is allowed to react with heating up to 120°C, as shown in Reaction Scheme 1, with amines of type R^1R^6NH in a protic solvent such as *n*-butanol, for 1 to 3 days, with the optional presence of an acid such as aqueous HCl, or a base such as Na_2CO_3, to provide compounds of the invention of the type depicted as formula (Ia). Compounds of the invention of formula (Ib) and (Ic) may be prepared by conducting similar reactions in a stepwise manner. For example, the first step is conducted in base to give either the compound of formula (IV) or formula (V), depending on the amine of type selected (R^1R^6NH or R^4R^5NH) as co-reactant. Subsequent reaction of (IV) or (V) with a second amine of type R^4R^5NH or R^1R^6NH, with heating and acid catalysis, provides the compounds of formula (Ib) or (Ic), respectively. Intermediate (V) is reacted with hydrazine followed by reaction with appropriate aryl aldehyde to compounds of the formula •(1d).

Reaction Scheme 2



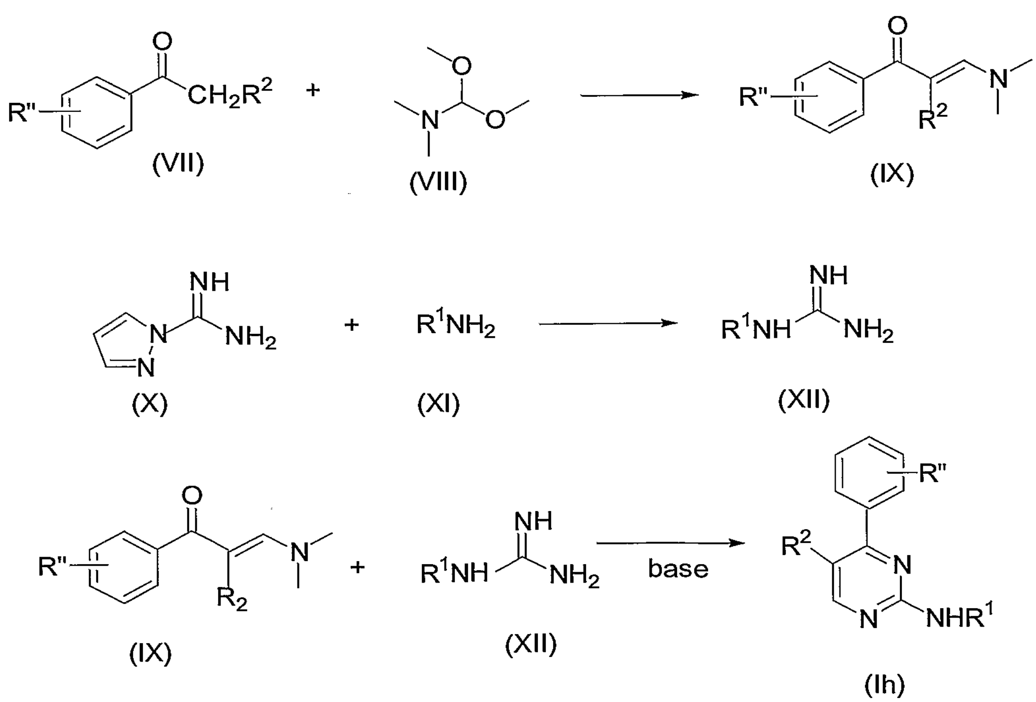
Compounds of the invention of formula (Ie), (If) and (Ig) are also prepared from the intermediate of formula (III) as shown in Reaction Scheme 2. For example, reaction of (III) with a nitrile, represented by $ArCH_2CN$, where Ar is a aryl or heteroaryl radical, in the presence of a strong base such as NaH, provides the

chloropyrimidine of formula (VIa); reaction of (VIa) with an amine of type R^1R^6NH, as previously described in Reaction Scheme 1, gives the compound of the invention of formula (Ie).

Intermediate (III) may react under a Suzuki-type coupling conditions (a palladium catalyst, and a base such as Na_2CO_3) with a boronic acid of type $R^4B(OH)_2$ to give a chloropyrimidine of formula (VIb). This formula (VIb) compound may undergo reaction with an amine of type R^1R^6NH, as previously described in Reaction Scheme 1, to give the compounds of the invention of formula (If).

The compound of formula (IV), as previously described in Reaction Scheme 1, may be allowed to react with a boronic acid of type $R^4B(OH)_2$ under the Suzuki-type coupling conditions described above to give the compound of the invention of formula (Ig).

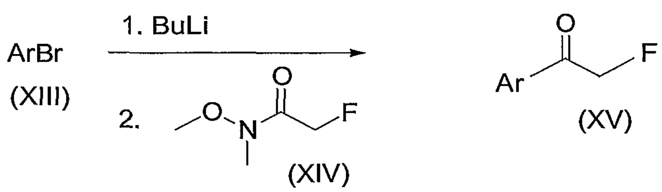
Reaction Scheme 3



Another type of compound of the invention, formula (Ih), is prepared as shown in Reaction Scheme 3. In this scheme, a ketone of formula (VII) (wherein R'' is methyl, methoxy, $-O-CH_2-O-$, fluoro, CN, or NO_2) reacts with DMF-

dimethylacetal of formula (VIII) in a refluxing solvent such as toluene to give an enaminone intermediate of formula (IX). A guanidine of formula (XII) is also prepared from an amine of formula (XI) and the reagent of formula (X) by heating the two together in a higher boiling solvent such as toluene/acetic acid mixtures. Reaction of the enaminone (IX) with the guanidine (XII) in a protic solvent such as methanol and a base such as sodium methoxide gives the compound of the invention of formula (Ih).

Reaction Scheme 4



Ketones of formula (VII) that are not commercially available may be conveniently prepared by the method illustrated in Reaction Scheme 4. An aryl or heteroaryl bromide of formula (XIII) may be converted to an aryllithium intermediate by halogen-metal exchange with butyllithium; reaction of the intermediate with an amide such as the compound of formula (XIV) provides the corresponding ketone of formula (XV).

Additional compounds of formula (I) may be prepared from other formula (I) compounds by elaboration of functional groups present. Such elaboration includes, but is not limited to, hydrolysis, reduction, oxidation, alkylation, acylation, esterification, amidation and dehydration reactions. Such transformations may in some instances require the use of protecting groups by the methods disclosed in T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis* (Wiley, New York, 1999), incorporated herein by reference. Such methods would be initiated after synthesis of the desired compound or at another place in the synthetic route that would be readily apparent to one skilled in the art.

Experimental Examples

The following specific preparative examples are included as illustrations of preparation of specific compounds of the invention, and are not to be construed as limiting the scope of the invention in any way.

LC-MS instrumentation:

(a) a Gilson HPLC system equipped with two Gilson 306 pumps, a Gilson 215 Autosampler, a Gilson diode array detector, a YMC Pro C-18 column (2 x 23mm, 120 A), and a Micromass LCZ single quadrupole mass spectrometer with z-spray electrospray ionization. Spectra were scanned from 120-800 amu over 1.5 seconds. ELSD (Evaporative Light Scattering Detector) data was also acquired as an analog channel.

(b) a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source.

HPLC conditions:

Method 1. Eluents were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonitrile with 0.02% TFA. Elution conditions consisted of a flow rate of 1.0 mL/min with an initial hold at 10% B for 0.5 min, followed by gradient elution from 10% B to 95% B over 3.5 min, followed by a final hold at 95% B for 0.5 min. Total run time was 6.5 min.

Method 2. Eluents as above; elution at a flow rate of 1.5 mL/min with an initial hold at 10% B for 0.5 min, followed by gradient elution from 10% B to 90% B over 3.5 min, followed by a final hold at 90% B for 0.5 min. Total run time was 4.8 min.

Abbreviations and Acronyms

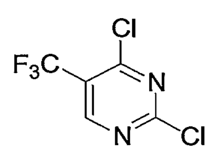
When the following abbreviations are used herein, they have the following meaning:

Ac_2O	acetic anhydride
anhy	anhydrous
BOC	*tert*-butoxycarbonyl
n-BuOH	*n*-butanol
t-BuOH	*tert*-butanol
t-BuOK	potassium *tert*-butoxide
CDI	carbonyl diimidazole
CD_3OD	methanol-d_4
Celite®	diatomaceous earth filter agent, ®Celite Corp.
CI-MS	chemical ionization mass spectroscopy
conc	concentrated
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
dec	decomposition
DIA	diisopropyl amine
DIBAL	diisobutylaluminum hydroxide
DMAP	4-(*N,N*-dimethylamino)pyidine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ELSD	evaporative light scattering detector
ES-MS	electrospray mass spectroscopy
EtOAc	ethyl acetate
EtOH	ethanol (100%)
EtSH	ethanethiol
Et_2O	diethyl ether
Et_3N	triethylamine
GC-MS	gas chromatography-mass spectroscopy
h	hour
HPLC	high performance liquid chromatography

IPA	isopropylamine
LAH	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectroscopy
LDA	lithium diisopropylamide
m/z	mass-to-charge ratio
MeCN	acetonitrile
NBS	*N*- bromosuccinimide
NMM	4-methylmorpholine
$PdCl_2dppf$	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd(OAc)_2$	palladium acetate
$P(O)Cl_3$	phosphorous oxychloride
PS-DIEA	Polystyrene-bound diisopropylethylamine
Rf	retention factor (TLC)
RT	retention time (HPLC)
rt	room temperature
TEA	triethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFFH	Fluoro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate
TLC	thin layer chromatography
TMAD	*N,N,N',N'*-tetramethylethylenediamine
TMSCl	trimethylsilyl chloride

Preparation of 2,4-dichloro-5-substituted pyrimidine starting materials:

Preparation of 2,4-dichloro-5-(trifluoromethyl)pyrimidine



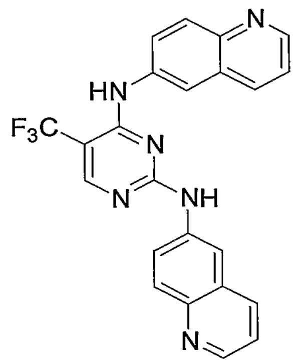
$POCl_3$ (25 mL) was mixed with DMF (0.5 mL). After the mixture cooled to room temperature, 5-trifluoromethyl uracil was added and the resulted mixture was heated to 110°C overnight. The reaction mixture was then cooled to room

temperature again and added slowly to ice water. The aqueous solution was then extracted by dichloromethane. The extracts were dried over magnesium sulfate and evaporated to dryness. The crude product was purified by preparative TLC (20% EtOAc in methylene chloride) to give 585 mg of the object compound.

Using this procedure and the appropriately substituted uracils as starting materials, 2,4-dichloro-5-fluoropyrimidine, 2,4-dichloro-5-bromopyrimidine and 2,4-dichloro-5-methylpyrimidine were similarly prepared.

Example 1

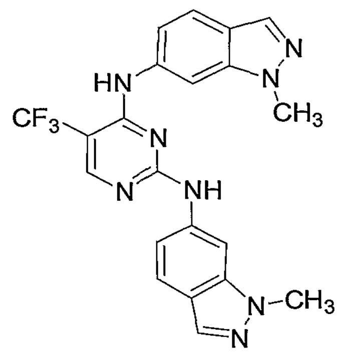
Preparation of *N*-(6-quinolinyl)-*N*-[2-(6-quinolinylamino)-5-(trifluoromethyl)-4-pyrimidinyl]amine



To an 8-mL vial was added 6-aminoquinoline (1.67 mmol), 2,4-dichloro-5-trifluoromethylpyrimidine (0.67 mmol), butanol (5 mL) and Na_2CO_3 (2 equiv). The mixture was heated to 120°C for 3 days, followed by evaporation to dryness. The residue was then dissolved in DMF and separated by preparative TLC (5% methanol in dichloromethane). LC-MS:RT 2.07; $[M+H]^+$ 433.

Example 2

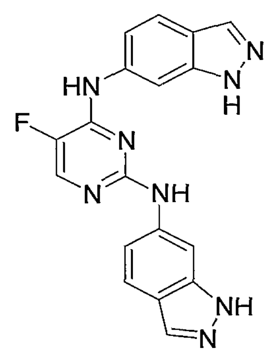
Preparation of *N*-(1-methyl-1*H*-indazol-6-yl)-*N*-{5-methyl-2-[(1-methyl-1*H*-indazol-6-yl)amino]-4-pyrimidinyl}amine



To an 8-mL vial was added (1-methyl-indazole-6-amine, 0.245 g, 1.67 mmol), 2,4-dichloro-5-trifluoromethylpyrimidine (0.11 g, 0.67 mmol), *n*-butanol (5 mL) and HCl (0.1 N, cat. amount). The mixture was heated to 120 °C for 3 days, followed by evaporation to dryness. The residue was then dissolved in DMF and separated by preparative TLC (5% methanol in dichloromethane). LC-MS: RT 1.64 min; $[M + H]^+$ 388.

Example 3

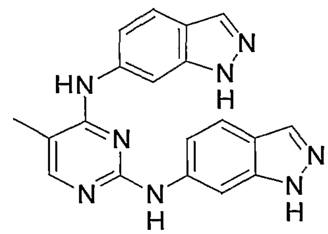
Preparation of *N*-[5-fluoro-2-(1*H*-indazol-6-ylamino)-4-pyrimidinyl]-*N*-(1*H*-indazol-6yl)amine



A mixture of 2, 4-dichloro-5-fluoro-pyrimidine (16.6 mg, 0.1 mmol) and 6-aminoindazole (39.9 mg, 0.3 mmol) in *n*-BuOH (2-3 mL) was heated at 120 °C with shaking for 48 h. The mixture was cooled to room temperature and purified by prep-TLC. LC-MS: RT 1.73 min; $[M+H]^+$ 361.

Example 4

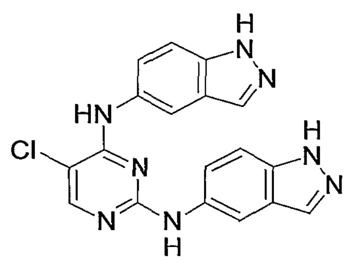
Preparation of *N*-(1*H*-indazol-6-yl)-*N*-[2-(1*H*-indazol-6-ylamino)-5-methyl-4-pyrimidinyl]amine



A mixture of 2,4-dichloro-5-methylpyrimidine (2.50 g, 9.6 mmol), 6-aminoindazole (3.2 g, 24.1 mmol) and catalytic amount of 1N HCl in *n*-BuOH was heated to 110°C for 24 h. The solvent was removed by evaporation under reduced pressure. The crude product was purified by silica gel column (gradient, ethyl acetate/hexane, 50/50 to 90/10) to afford the object compound (2.95 g, 67%) as an off-white powder. HPLC/MS: $(M+H)^+$ 357.48 *m/z.* Retention time (HPLC/MS) = 1.98 min. ^1H NMR (DMSO-d_6): δ12.86 (1H, s); 12.61 (1H, s); 9.14 (1H, s); 8.43 (1H, s); 8.11 (1H, s); 7.99 (2H, d); 7.86(2H, s); 7.70 (1H, d); 7.51(2H, m); 7.37 (1H, d); 2.15 (3H, s).

Example 5

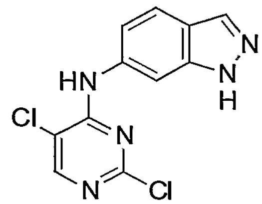
Preparation of *N*-[5-chloro-2-(1*H*-indazol-5-ylamino)-4-pyrimidinyl]-*N*-(1*H*-indazol-5-yl)amine



A mixture of 2,4,5-trichloro-pyrimidine (200 mg, 1.09 mmol), 5-aminoindazole (363 mg, 2.72 mmol) and catalytic amount of 1N HCl was heated to 120 °C for 24 h. The solvent was removed by evaporation under reduced pressure. The crude product was purified by silica gel column (gradient, ethyl acetate/hexane, 50/50 to 8/20) to afford the target compound) (102mg, 25%) as yellow powder. HPLC/MS: $(M+H)^+$ 377 *m/z.* Retention time (HPLC/MS) = 1.86 min.

Example 6

Preparation of *N*-(2,5-dichloro-4-pyrimidinyl)-1*H*-indazol-6-amine intermediate:

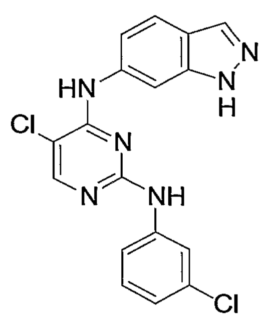


In a 250 mL round bottom flask was placed 2,4,5-trichloropyrimidine (5.0 g, 27.2 mmol), sodium carbonate (17.3 g, 163.2 mmol) and 6-aminoindazole (3.63 g, 27.2 mmol) in 136 mL of ethanol. The reaction mixture was stirred at room temperature overnight. An insoluble white solid was filtered, suspended in water (50 mL), stirred at room temperature for 1-2 h and then filtered, washed with acetonitrile and dried in an oven to provide 6.41 g of the desired compound.

An additional 0.5 g was recovered from the filtrate. Total yield was 90.7%. GC/MS 280.2 (M+1) RT = 2.38 min; ^{1}H-NMR (DMSO-d_6) δ 13.061 (s, 1H); 9.578 (s, 1H); 8.382 (s, 1H); 8.020 (s, 1H); 7.850 (s, 1H); 7.705-7.735 (d, 1H); 7.267-7.302 (d, 1H).

Example 7

Preparation of *N*-{5-chloro-2-[(3-chlorophenyl)amino]-4-pyrimidinyl}-*N*-(1*H*-indazol-6-yl)amine

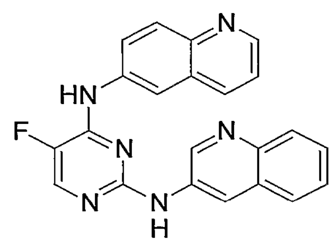


In a 8 mL vial were placed *N*-(2,5-dichloro-4-pyrimidinyl)-1*H*-indazol-6-amine from Example 6 (64.4 mg, 0.23 mmol), 3-chloroaniline (58.7 mg, 0.46 mmol) and 1 mL of 1N HCl solution. The vial was capped under argon and shaken at 100 °C overnight. Upon cooling, white solid crystallized out of solution and was simply removed by filtration. The crude white solid was dissolved in methanol, absorbed on silica gel, dried, and chromatographed with

CH_2Cl_2/methanol (100/2) to provide 44 mg of a white solid target compound (51.5 %). GC/MS 371.3 (M+1) RT = 2.73 min; ^{1}H-NMR (DMSO-d_6) δ 12.962 (s, 1H); 9.531 (s, 1H); 9.075 (s, 1H); 8.262 (s, 1H); 8.003 (s, 1H); 7.706-7.765 (m, 2H); 7.646 (s, 1H); 7.468-7.488 (d, 1H); 7.309-7.349 (d, 1H); 7.012-7.071 (t, 1H); 6.813-6.853 (d, 1H).

Example 8

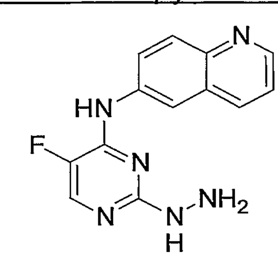
Preparation of *N*-[5-fluoro-2-(3-quinolinylamino)-4-pyrimidinyl]-*N*-(6-quinolinyl)amine



In a 15 mL round bottom flask were placed *N*-(2-chloro-5-fluoro-4-pyrimidinyl)-6-quinolinamine (63.2 mg, 0.23 mmol, obtained by the method of Example 6), 3-aminoquinoline (66.3 mg, 0.46 mmol), 1.5 mL of 1-butanol and 0.5 mL of 1N HCl solution. The mixture was heated at 128-130 °C overnight. The reaction mixture was evaporated to dryness and the residue was dissolved in methanol, absorbed on silica gel, dried and chromatographed with CH_2Cl_2/methanol (100/5) to provide 36.7 mg of a white solid of the target product (44%). GC/MS 383.4 (M+1) RT = 1.89 min; ^{1}H-NMR (DMSO-d_6) δ 9.821 (s, 2H); 9.012 (s, 1H); 8.805 (s, 1H); 8.635 (s, 1H); 8.504 (s, 1H); 8.278 (s, 1H); 8.052-8.146 (m, 2H); 7.976-8.014 (d, 1H); 7.864-7.920 (d,1H); 7.373-7.525 (m, 4H).

Example 9

Preparation of *N*-(5-fluoro-2-hydrazino-4-pyrimidinyl)-6-quinolinamine intermediate



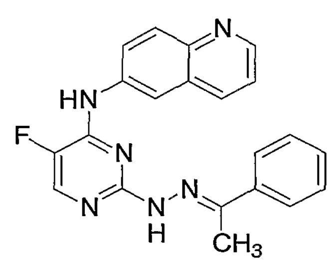
In a 25 mL round bottom flask was placed 2,4-dichloro-5-fluoropyrimidine (1.0 g, 6.0 mmol, 1 equiv) and 6-aminoquinoline (0.95 g, 6.6 mmol, 1.1 equiv) in

10 mL of THF. To this was added K_2CO_3 (0.83 g, 6.0 mmol, 1 equiv) and 2 mL of H_2O. This was heated to 60 °C overnight at which point TLC revealed no remaining starting material. The volatiles were removed under reduced pressure and the residue allowed to stir in 50 mL of H_2O. The remaining solids were filtered to provide 1.84 g of *N*-(2-chloro-5-fluoro-4-pyrimidinyl)-6-quinolinamine as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.50 (dd, 1H), 8.02 (m, 2H), 8.27 (d, 1H), 8.30 (m, 1H), 8.40 (d, 1H), 8.81 (dd, 1H), 10.30 (s, 1H); LC/MS/+esi 275.4 $[M+H]^+$.

In a 50 mL round-bottomed flask was placed 1.0 g (3.6 mmol) of *N*-(2-chloro-5-fluoro-4-pyrimidinyl)-6-quinolinamine in 18 mL of EtOH. To this was added 0.73 g (14.5 mmol, 4 equiv) of hydrazine monohydrate and the reaction was allowed to reflux overnight. The reaction was allowed to cool to room temperature and 20 mL of H_2O was added, resulting in a white precipitate. This was filtered to yield 0.78 g of the desired pure compound as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.85 (br s, 2H), 7.08 (dd, 1H), 7.52 (m, 2H), 7.66 (m, 2H), 7.91 (d, 1H), 8.35 (m, 1H), 8.47 (d, 1H), 9.16 (s, 1H); LC/MS/+esi 271.5 $[M+H]^+$.

Example 10

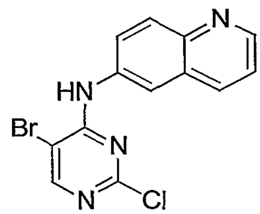
Preparation of derivatives of benzaldehyde [5-fluoro-4-(6-quinolinylamino)-2-pyrimidinyl]hydrazone



In a 8 mL amber vial was placed *N*-(5-fluoro-2-hydrazino-4-pyrimidinyl)6-quinolinamine prepared according to Example 9 (50 mg, 0.19 mmol) in 2 mL of anhydrous EtOH. To this was added 0.20 mmol (1.1 equiv) acetophenone, and the vial was capped under argon and shaken on a reflux block for 0.5 h. This resulted in precipitate formation. The solids were filtered and rinsed with EtOH to provide the pure desired product in 70-80% yield. LC-MS: RT: 2.19 min.

Example 11

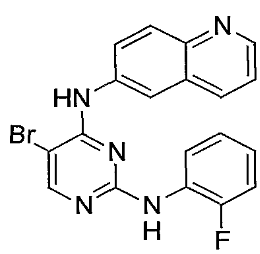
Preparation of *N*-(5-bromo-2-chloro-4-pyrimidinyl)-6-quinolinamine intermediate



To 2,4-dichloro-5-bromopyrimidine (10 g, 44 mmol) in ethanol (100 mL) was added 6-aminoquinoline (6.33 g, 44 mmol) and sodium carbonate (28 g, 0.26 mol) at room temperature. The reaction was stirred for 18 h and then quenched with water (100 mL). Diethyl ether (300 mL) was added to the mixture resulting in the formation of a precipitate. The solids were filtered then washed with water (50 mL) and diethyl ether (200 mL). The tan powder was dried to yield 12.5 g of the target compound (37 mmol, 85%). The product was taken directly to the next step.

Example 12

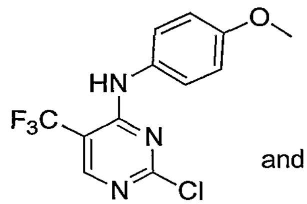
Preparation of *N*-{5-bromo-2-[(2-fluorophenyl)amino]-4-pyrimidinyl}-*N*-(6-quinolinyl)amine:



To *N*-(5-bromo-2-chloro-4-pyrimidinyl)-6-quinolinamine obtained according to the method of Example 11 (100 mg, 0.30 mmol) in butanol (2 mL) was added 2-fluoroaniline (80 mg, 0.31 mmol), followed by 1N HCl (2 mL). The reaction was heated to 115 °C for 26 h. The reaction was cooled to room temperature and then concentrated to yield the crude product. The product was chromatographed with 20% ethyl acetate in hexane yielding the target compound as a tan powder (65 mg, 52%). Rf = 0.61 (CH_2Cl_2/MeOH = 95/5). ^{1}H NMR (DMSO-d_6) δ 9.42-9.45 (2H, m),), 9.09-9.12 (1H, m), 8.73-8.78 (1H, m), 8.63 (1H, s), 8.21-8.38 (3H, m), 7.94-7.98 (1H, dd, J = 1.2, 2.7Hz), 7.55-7.62 (1H, m), 6.97-7.21 (3H, m).

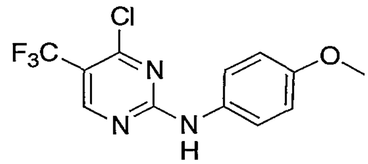
Example 13

Preparation of the mixture of two intermediate isomers: 2-chloro-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)-4-pyrimidinamine (A) and 4-chloro-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)-2-pyrimidinamine (B)



(A)

and

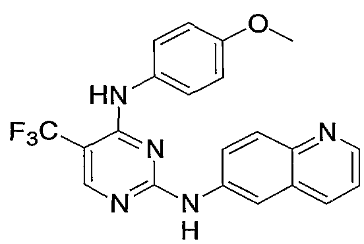


(B)

A suspension of 2,4-dichloro-5-trifluoromethylpyrimidine (3.90 mmol, 1 equiv), 4-methoxyaniline (3.90 mmol, 1 equiv), and sodium carbonate (16.6 mmol, 6 equiv) in 10 mL of ethanol was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified by flash column chromatography (20% ethyl acetate in hexane) which gave a mixture of (A) and (B). Total yield 95 %.

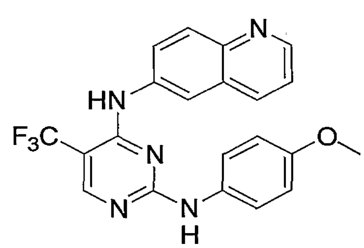
Example 14

Preparation of the mixture of two isomers: *N*-(4-methoxyphenyl)-*N*-[2-(6-quinolinylamino)-5-(trifluoromethyl)-4-pyrimidinyl]amine (C) and *N*-(4-methoxyphenyl)-*N*-[4-(6-quinolinylamino)-5-(trifluoromethyl)-2-pyrimidinyl]amine (D)



(C)

and



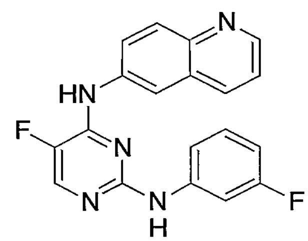
(D)

A suspension of isomeric mixture of (A) and (B) obtained according to Example 13 (0.33 mmol, 1 equiv) and 6-aminoquinoline (0.66 mmol, 2 equiv) in

2.7 mL of butanol and 1.3 mL of 1N HCl was shaken at 120 °C overnight. The reaction was concentrated, and the isomers (C) and (D) were separated by HPLC purification on a funnel and washed with cold EtOH and dried in vacuo.

Example 15

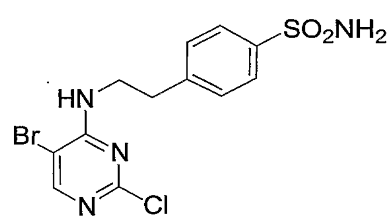
Preparation of N-{5-fluoro-2-[(3-fluorophenyl)amino]-4-pyrimidinyl}-N-(6-quinolinyl)amine



N-(2-Chloro-5-fluoro-4-pyrimidinyl)-6-quinolinamine, (1 equiv) obtained by the method of Example 6 from 2,4-dichloro-5-fluoropyrimidine and 6-quinolinamine, and 3-fluoroaniline (2 equiv) were suspended in *n*-BuOH and heated at 120 °C overnight for 2 days. The pure product was obtained by column Chromatography. LC-MS: RT 1.64 min; $[M+H]^+$ 350.

Example 16

Preparation of 4-{2-[(5-bromo-2-chloro-4-pyrimidinyl)amino]ethyl}-benzenesulfonamide intermediate

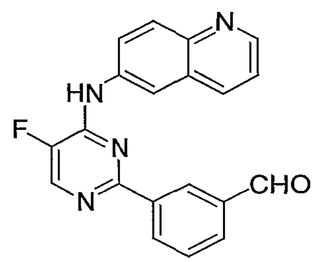


A solution of 4-(2-aminoethyl)benzenesulfonamide (1.7 g, 8.5 mmol), 5-bromo-2,4-dichloropyrimidine (1.8 g, 7.9 mmol), and sodium carbonate in ethanol was stirred at rt overnight. LC-MS showed the major peak as the desired product. The solvent was removed in vacuo. The residue was added to water, and extracted with ethyl acetate several times. The organic layer was dried over magnesium sulfate and filtered. The solution was evaporated until a small amount of solid precipitated out. After standing at rt for several h, more solid crystallized

out. LC-MS shows two regioisomers. The material was then recrystallized from ethyl acetate to give the desired regioisomer (1.2 g, 31%).

Example 17

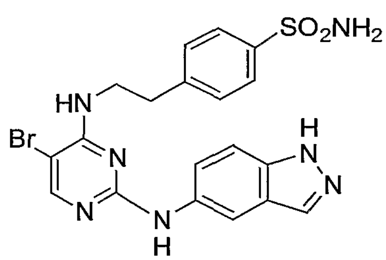
Preparation of 3-[5-fluoro-4-(6-quinolinylamino)-2-pyrimidinyl]benzaldehyde



N-(2-Chloro-5-fluoro-4-pyrimidinyl)-6-quinolinamine (1 equiv), obtained from 5-fluoro-2, 4-dichloro-pyrimidine and 6-quinolinamine by the method of Example 6, was treated with 3-formylphenylboronic acid (1.2 equiv) in the presence of $PdCl_2dppf$ (0.06 equiv) and Na_2CO_3 (2 equiv), in ethylene glycol ether and water (4:1 v/v) at 60 °C for 2-6 h. The reaction mixture was evaporated to dryness. The residue was purified by silica gel chromatography (EtOAc-Hexane) to give the pure product. LCMS: RT 1.93 min; $[M+H]^+$ 345.

Example 18

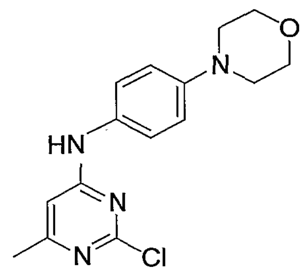
Preparation of 4-(2-{[5-bromo-2-(1*H*-indol-5-ylamino)-4-pyrimidinyl]amino} ethyl)benzenesulfonamide



A solution of 4-{2-[(5-bromo-2-chloro-4-pyrimidinyl)amino]ethyl-benzenesulfonamide (50 mg, 0.13 mmol), 1*H*-indazol-5-amine, and a catalytic amount of hydrochloride acid in 1-butanol (3 mL) was heated at 115 °C overnight. Some yellow solid precipitated out. The solution was filtered. The filtrate was washed with a small amount of methanol and ethyl acetate to give a yellow solid (42.3 mg, 68.0%).

Example 19

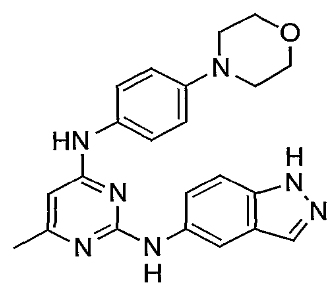
Preparation of 2-chloro-4-*N*-(4-morpholinophenyl)-6-methylpyrimidine



To a solution of 4-morpholinoaniline (0.535 g, 3.00 mmol) in ethanol (20 mL) was added 2,4-dichloro-6-methylpyrimidine (0.978 g, 6.00 mmol) and Na_2CO_3 (1.59 g, 15 mmol). After mixing at room temperature for 72 h, the reaction was concentrated in vacuo. The solids were washed with hexanes (3 x 10 mL) and water (10 mL), filtered, and dried under high vacuum to afford the title compound (0.894 g, 97% crude yield) as a slightly purple solid. HPLC/MS: $(M+H)^+$ 305.28 *m/z.* Retention time (HPLC/MS) = 0.37 min.

Example 20

Preparation of 2-*N*-5'-aminoindazole-4-(4-morpholinophenyl)-6-methylpyrimidine

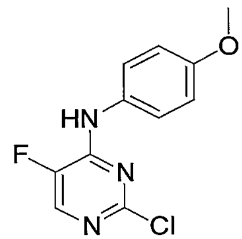


To a solution of 2-chloro-4-*N*-(4-morpholinophenyl)-6-methylpyrimidine obtained according to the process of Example 19 0.305 g, 1.00 mmol) in *n*-butanol (10 mL) was added 5-aminoindazole (0.266 g, 2.00 mmol) and HCl (4.0M in 1,4-dioxane, 50 μL, 0.20 mmol). The mixture was heated to 115 °C for 16 h. Upon cooling to room temperature, the precipitate was filtered and recrystallized from EtOH. This afforded 0.1495 g (37% yield) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 9.06 (s, 1H), 8.99 (s, 1H), 8.27 (s, 1H), 7.88 (s, 1H), 7.4-7.6 (m, 4H), 6.91 (d, 2H, J=9.2Hz), 5.97 (s, 1H), 3.77 (m, 4H), 3.08 (m, 4H),

2.19 (s, 3H). HPLC/MS: $(M+H)^+$ 402.22 *m/z*. Retention time (HPLC/MS) = 1.13 min.

Example 21

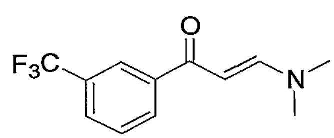
Preparation of 2-chloro-5-fluoro-*N*-(4-methoxyphenyl)-4-pyrimidinamine intermediate



A suspension of 2,4-dichloro-5-fluoropyrimidine (8.98 mmol, 1 equiv), 4-methoxyaniline (8.98 mmol, 1 equiv), and sodium carbonate (53.9 mmol, 6 equiv) in 10 mL of ethanol was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The resulting residue was used without further purification. Total yield was 88%.

Example 22

Preparation of (2E)-3-(dimethylamino)-1-[3-(trifluoromethyl)phenyl]-2-propen-1-one intermediate

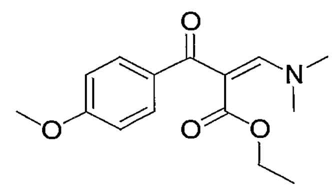


A suspension of 3'-(trifluoromethyl)acetophenone (6.0 g, 31.9 mmol) and *N,N*-dimethylformamide dimethyl acetal (3.8 g, 31.9 mmol) in toluene (35 mL) was heated at reflux overnight. The yellow solution was cooled to room temperature and concentrated under reduced pressure. The crude material was coated on silica and purified by column chromatography (100% CH_2Cl_2) to afford the desired product as a yellow solid (6.1 g; 25.1 mmol; 79% yield); ^1H NMR (DMSO-d_6) 8.19 (d, $J = 7.6$ *Hz*, 1H), 8.15 (s, 1H), 7.83 (d, $J = 7.9$ *Hz*, 1H), 7.78 (d, $J = 12$ *Hz*, 1H),

7.66 (t, *J = 7.9 Hz*, 1H), 5.89 (d, *J = 11.7 Hz*, 1H), 3.15 (s, 3H), 2.94 (s, 3H); ES MS $(M+H)^{+}$= 244.1.

Example 23

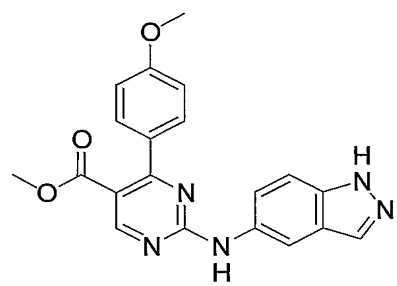
Preparation of ethyl (2Z)-3-(dimethylamino)-2-(4-methoxybenzoyl)-2-propenoate intermediate



The enamine was prepared according to the process of Example 22 using ethyl 4-methoxybenzoyl acetate to afford the desired product as an orange oil which was used without further purification; MS (ES) 278.0 $(M+H)^{+}$.

Example 24

Preparation of methyl 2-(1*H*-indazol-5-ylamino)-4-(4-methoxyphenyl)-5-pyrimidinecarboxylate

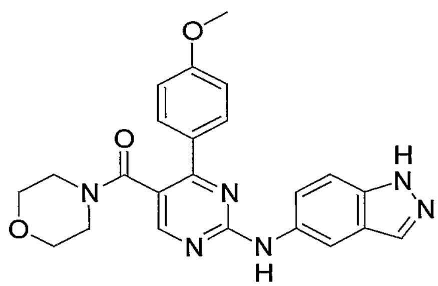


A mixture of ethyl (2Z)-3-(dimethylamino)-2-(4-methoxybenzoyl)-2-propenoate obtained according to the process of Example 23 (500 mg, 1.8 mmol), *N*-(1*H*-indazol-5-yl)ethanimidamide diacetate obtained by reaction of indazole-5-amine (1 equiv) and 1H-pyrazole-1-carboxamidine hydrochloride. (532 mg, 1.8 mmol), and 0.5 M sodium methoxide in MeOH (10.8 mL) in MeOH (7.2 mL) were heated at reflux overnight. The reaction was cooled to rt and quenched with H_2O (2 mL). The mixture was made neutral with the addition of 1N HCl and extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was recrystallized from MeOH and dried in vacuo at 45°C to afford the desired product

as a tan solid (147 mg, 0.39 mmol; 22% yield); mp 218-221 °C; TLC (DCM/MeOH, 95:5): R_f = 0.39.

Example 25

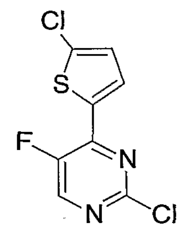
Preparation of *N*-[4-(4-methoxyphenyl)-5-(4-morpholinylcarbonyl)-2-pyrimidinyl]-1*H*-indazol-5-amine



To a solution of morpholine (116 mg, 1.3 mmol) in toluene (5 mL) was added 2M trimethylaluminum in toluene (670 µL), dropwise. The mixture was stirred until gas evolution ceased (approximately 45 min). The preformed aluminum amide was then added dropwise to a suspension of methyl 2-(1*H*-indazol-5-ylamino)-4-(4-methoxyphenyl)-5-pyrimidinecarboxylate obtained according to the process of Example 24 (100 mg, 0.27 mmol) in toluene (5 mL). The reaction was allowed to stir at reflux for 2 h. The heat was removed and the reaction was allowed to stir at rt overnight. The mixture was then heated at reflux for an additional 6 h. The mixture was cooled to rt and was quenched with the addition of 1N HCl (2 mL). The heterogeneous mixture was filtered through Extrelut and the filtering aid was washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure. The crude product was purified by preparative HPLC (C_{18} ODS, 10-90% CH_3CN/H_2O, 0.1% TFA) and dried in vacuo at 50°C to afford the desired product as a tan solid (61 mg, 0.14 mmol; 53% yield); mp152-154 °C; MS (ES) 431.3 $(M+H)^+$.

Example 26

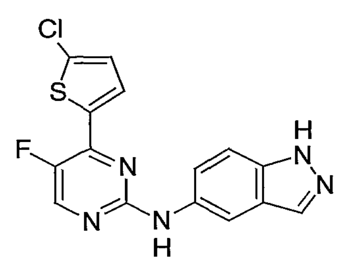
Preparation of 2-chloro-4-(5-chloro-2-thienyl)-5-fluoropyrimidine intermediate



A mixture of 2,4-dichloro-5-fluoropyrimidine (0.834 g, 5.00 mmol) and $NaHCO_3$ (1.26 g, 15.0 mmol) in 1,2-dimethoxyethane:water (4:1, 15 mL) was degassed with Argon for 30 min at room temperature. This solution was slowly heated to reflux, and 5-chloro-2-thiophene boronic acid (0.812 g, 5.0 mmol, Lancaster) and tetrakis(triphenylphospine)-palladium(0) (0.578 g, 5.00 mmol) were added. After 16 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. 20 mL of H_2O was added and the crude product was extracted with ethyl acetate (3 x 40 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by silica gel column chromatography (1% ethyl acetate/hexanes to 10% ethyl acetate/hexanes gradient) to afford 0.025 g (2%) of the title compound as a slightly green solid. LC-MS: $(M+H)^+$ 247.9 *m/z*. Retention time (LC-MS): 3.22 min.

Example 27

Preparation of *N*-[4-(5-chloro-2-thienyl)-5-fluoro-2-pyrimidinyl]-1*H*-indazol-5-amine

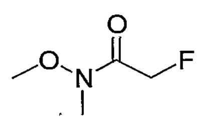


5-Aminoindazole (0.020 g, 0.20 mmol) was added to a mixture of 5-chloro-2-(2-chloro-5-fluoropyrimidin-4-yl)thiophene (0.025 g, 0.10 mmol) in *n*-butanol (1 mL). Catalytic HCl (0.002 mL) was added, and the reaction mixture was heated to 115 °C. After 16 h the solvent was removed in vacuo, and the product was purified by preparative HPLC (10% acetonitrile, 90% water, 0.1% TFA to 90%

acetonitrile, 10% water, 0.1% TFA gradient) to afford 0.0036 g of A (10%) as a brownish solid. LC/MS: $(M+H)^+$ 345.1 *m/z*. Retention time (LC-MS): 2.96 min. ^1H NMR (DMSO-d_6) δ 9.74 (s, 1H), 8.62 (d, 1H, J = 3.2 Hz), 8.16-8.17 (m, 1H), 8.03 (s, 1H), 7.74-7.75 (dd, 1H, J = 1.4 Hz, J = 2.8 Hz), 7.55-7.58 (dd, 1H, J = 2.0 Hz, J = 9.2 Hz), 7.49 (d, 1H, J = 9.2 Hz), 7.32 (d, 1H, J = 4.0 Hz).

Example 28

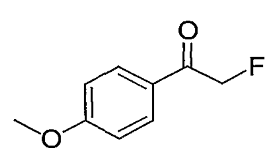
Preparation of 2-fluoro-*N*-methoxy-*N*-methylacetamide intermediate



To a stirred –10°C solution of *N,O*-dimethylhydroxylamine hydrochloride (18.4 g, 189 mmol) in dichloromethane (175 mL) was added 2.0M trimethyl aluminum (94.5 mL, 189 mmol) dropwise via an addition funnel. This was slowly warmed to rt and stirred for 1h. This solution was then added dropwise to a –10 °C solution of ethyl fluoroacetate (10.0 g, 94.3 mmol) in dichloromethane (100 mL). This was warmed to rt and stirred for 18 h. 1M Rochelle's salt (50 mL) was added slowly and this was stirred for 1 h. The reaction mixture was then diluted with H_2O and the layers were separated. The aqueous layer was extracted with dichloromethane (3 X 25 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 8.70 g (76%) of the desired product as a dark oil that was used without further purification.

Example 29

Preparation of 2-fluoro-1-(4-methoxyphenyl)ethanone intermediate

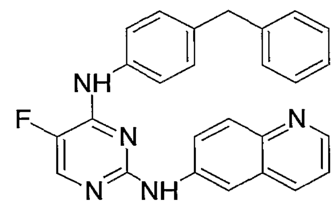


To a –78 °C solution of bromoanisole (2.7 mmol, 1.3 equiv) in 15 mL of THF was added 1.6 M *n*-BuLi (5.4 mmol, 2.6 equiv). This was stirred for 15 min and then added to a solution of 2-fluoro-*N*-methoxy-*N*-methylacetamide obtained according to the process of Example 28 (2.07 mmol, 1.0 equiv) in 15 mL of THF. The reaction was maintained at –78 °C for 45 min and then 5 mL of 1M HCl was

added. The reaction was diluted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and reduced. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to yield the desired product as a pure oil that solidified upon standing. Total yield 21%.

Example 30

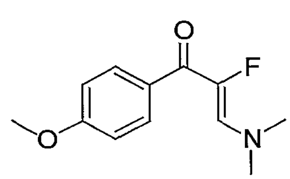
Preparation of *N*-(4-benzylphenyl)-*N*-[5-fluoro-2-(6-quinolinylamino)-4-pyrimidinyl]amine



N-(4-Benzylphenyl)-2-chloro-5-fluoro-4-pyrimidinamine, obtained from 5-fluoro-2,4-dichloropyrimidine and 4-benzylaniline using the method of Example 21, (1 equiv) was treated with 6-aminoquinoline (2 equiv), and suspended in 1N HCl. The mixture was heated at 100 °C for 7 days. Upon cooling to rt, the solution was neutralized with 2N Na_2CO_3 and extracted with *n*-BuOH. The organic layer was collected, and dried. The resulting crude product was purified by preparative TLC (60% EtOAc / Hexanes). LCMS: RT 2.18 min; $[M+H]^+$ 422.

Example 31

Preparation of (2Z)-3-(dimethylamino)-2-fluoro-1-(4-methoxyphenyl)-2-propen-1-one intermediate



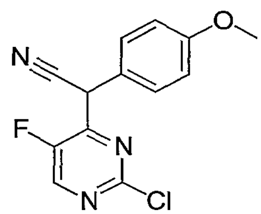
A solution of 2-fluoro-1-(4-methoxyphenyl)ethanone obtained according to the process of Example 29 (7.1 mmol, 1 equiv) and *N,N*-dimethylformamide dimethyl acetal (28.4 mmol, 4 equiv) was heated at 120 °C for 2 h. The reaction was diluted with water. The aqueous layer was extracted with ethyl acetate. The organic layers were separated, dried over sodium sulfate, filtered, and reduced. The residue was purified by flash column chromatography (75% ethyl acetate in

hexanes) to yield the desired product as a pure oil that solidified upon standing. Total yield 85.4%.

This intermediate was converted to the product of Example 375 using the procedure for Example 41.

Example 32

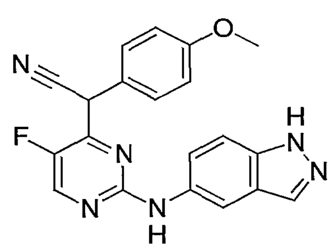
Preparation of (2-chloro-5-fluoro-4-pyrimidinyl)(4-methoxyphenyl)acetonitrile



A solution of p-methoxyphenylacetonitrile (381 µL, 2.7 mmol) in 4 mL of DMF at -15 °C was treated with sodium hydride (60% dispersion in mineral oil, 102 mg, 2.7 mmol) and allowed to react for 15 min. The suspension was then treated with 5-fluoro-2,4-dichloropyrimidine (296 mg, 1.78 mmol) and allowed to stir for 1.5 h at –15 °C and an additional 0.5 h at rt. The reaction was quenched with isopropanol and saturated ammonium chloride. Purification with silica gel chromatography gave a single regioisomer as a faintly yellow oil (346 mg, 70%).

Example 33

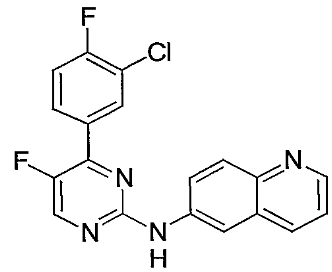
Preparation of [5-fluoro-2-(1*H*-indazol-5-ylamino)-4-pyrimidinyl](4-methoxyphenyl)acetonitrile



The compound was prepared by a method similar to that described for Example 18, using (2-chloro-5-fluoro-4-pyrimidinyl)(4-methoxyphenyl)acetonitrile, obtained according to Example 32, as the chloride.

Example 34

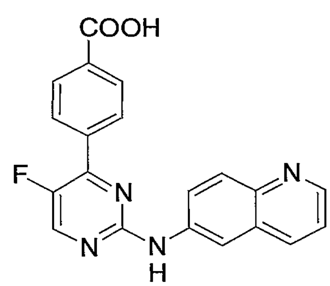
Preparation of *N*-[4-(3-chloro-4-fluorophenyl)-5-fluoro-2-pyrimidinyl]-6-quinolinamine



In a 15 mL flask were placed 2-chloro-4-(3-chloro-4-fluorophenyl)-5-fluoropyrimidine (130.0 mg, 0.5 mmol), 6-aminoquinoline (144.2 mg, 1.0 mmol), 3.4 mL of 1-butanol and 1.1 mL of 1N HCl solution. The mixture was heated at 128-130 °C for 2 days. The reaction mixture was evaporated to dryness and the residue was dissolved in methanol, absorbed on silica gel, dried and chromatographed with CH_2Cl_2/methanol = 100/3 to provide a mixture of the desired compound with trace impurities. This mixture was purified again by Prep.TLC with CH_2Cl_2/methanol (100/3) to give 9.3 mg of a yellow solid (5.1%). GC/MS 369.4 (M+1) RT = 2.65 min; ^{1}H-NMR (DMSO-d_6) δ 10.28 (s, 1H); 8.787 (s, 1H); 8.744 (s, 1H); 8.528 (s, 1H); 8.290-8.311 (d, 1H); 8.203-8.247 (d, 1H); 8.074-8.139 (m, 1H); 7.944 (s, 2H); 7.642-7.707 (t, 1H); 7.447-7.491 (m, 1H).

Example 35

Preparation of 4-[5-fluoro-2-(6-quinolinylamino)-4-pyrimidinyl]benzoic acid



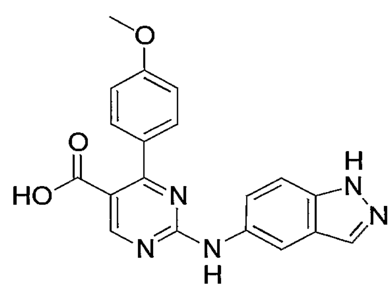
Step 1. To a solution of 2, 4-dichloro-5-fluoropyrimidine (500 mg, 3.0 mmol) in degassed DME/H_2O (9.3 mL/1.8 mL) was added 4-carbobutoxyphenyl boronic acid (244 mg, 1.1 equiv), followed by $PdCl_2$(dppf) (49 mg, 0.060 mmol).

The reaction was stirred at rt overnight. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (95:5 hexanes/ EtOAc) to afford the desired product which was verified by ^{1}H NMR and LC-MS and used directly in the next step.

Step 2. In a 8 mL vial were placed butyl 4-[5-fluoro-2-(6-quinolinylamino)-4-pyrimidinyl]benzoate obtained in Step 1 (6.3 mg, 0.015 mmol), methanol (0.75 mL) and 0.09 mL of 1N NaOH solution. The vial was shaken at 60 °C overnight. Upon cooling, the reaction mixture was acidified with 1N HCl to pH 1-2 and evaporated to dryness. To this residue was added water and the resulting precipitated solid was filtered, washed with water and methanol, and dried in an oven to provide 4.3 mg of an off-white solid (79.6%). GC/MS 361.3 (M+1) RT = 2.00 min; ^{1}H-NMR (DMSO-d_6) δ10.415 (s, 1H); 8.755-8.845 (m, 2H); 8.653 (s, 1H); 8.443-8.496 (d, 1H); 8.164-8.234 (m, 4H); 8.007-8.059 (m, 2H); 7.571-7.606 (m, 1H).

Example 36

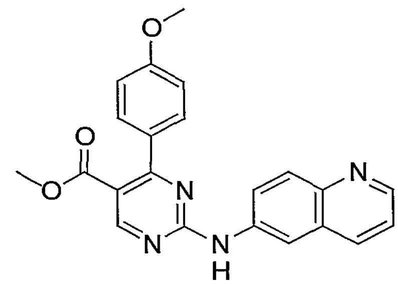
Preparation of 2-(1*H*-indazol-5-ylamino)-4-(4-methoxyphenyl)-5-pyrimidinecarboxylic acid



A solution of methyl 2-(1*H*-indazol-5-ylamino)-4-(4-methoxyphenyl)-5-pyrimidinecarboxylate (50 mg, 0.13 mmol) and 1N NaOH (0.13 mL) in MeOH/H_2O/THF (2 mL/0.13 mL/0.13 mL) was stirred at 50 °C overnight. The reaction was cooled to room temperature and the mixture was concentrated under reduced pressure. The residue was dissolved in H_2O and the pH was adjusted to 6 with the addition of 1N HCl. The resulting solid was collected by filtration and was dried in vacuo at 45 °C to afford the desired product (42 mg, 0.12 mmol; 87% yield); mp = 269-272 °C, MS (ES) 362.3 $(M+H)^+$; TLC (DCM/MeOH, 90:10): R_f = 0.40.

Example 37

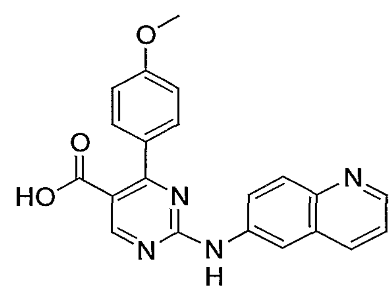
Preparation of methyl 4-(4-methoxyphenyl)-2-(6-quinolinylamino)-5-pyrimidinecarboxylate



The compound was prepared analogously to that described in Example 35, Step 1. The crude product was purified by preparative HPLC (C_{18} ODS, 10-90% CH_3CN/H_2O, 0.1%TFA) and dried in vacuo at 50 °C to afford the desired product as a white solid (30 mg, 0.078 mmol; 11% yield); mp 155-157 °C; MS (ES) 387.4 $(M+H)^+$.

Example 38

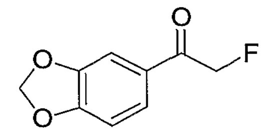
Preparation of 4-(4-methoxyphenyl)-2-(6-quinolinylamino)-5-pyrimidinecarboxylic acid



The product was prepared according to the process described for Example 36 using methyl 4-(4-methoxyphenyl)-2-(6-quinolinylamino)-5-pyrimidinecarboxylate obtained according to the process of Example 37. The product was triturated with CH_3CN and collected by filtration to afford the desired product as a yellow solid (21 mg, 0.056 mmol; 89% yield); mp = 216-220 °C; MS (ES) 373.4 $(M+H)^+$.

Example 39

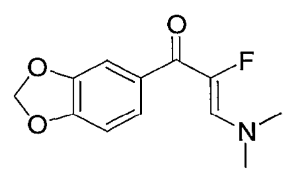
Preparation of 1-(1,3-benzodioxol-5-yl)-2-fluoroethanone



To a stirred –78 °C solution of 4-bromo-1, 2-(methylenedioxy) benzene (1.29 mL, 10.7 mmol) in THF (25 mL) was added 1.6M *n*-BuLi (13.4 mL) dropwise via syringe. This was stirred for 0.5 h then added dropwise to a stirred –78 °C solution of 2-fluoro-*N*-methoxy-*N*-methylacetamide obtained according to the process of Example 23 (1.00 g, 8.26 mmol) in THF (25 mL). The reaction was stirred for 1 h and then acidified to pH 2 with 1N HCl. The reaction mixture was diluted with EtOAc (25 mL) and H_2O (25 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude solid was recrystallized from hot EtOH to afford 387 mg (24%) of the desired product as off-white needles.

Example 40

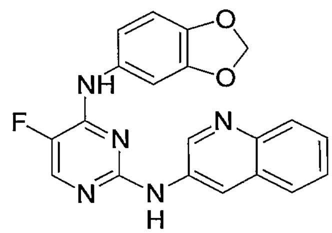
Preparation of (2Z)-1-(1,3-benzodioxol-5-yl)-3-(dimethylamino)-2-fluoro-2-propen-1-one



To a stirred solution of 1-(1,3-benzodioxol-5-yl)-2-fluoroethanone obtained according to the process of Example 39 (300 mg, 1.65 mmol) in DMF (20 mL) was added Bredereck's reagent (0.476 mL, 2.31 mmol). This was warmed to 120 °C and stirred for 20 h. The reaction mixture was cooled to rt and then diluted with EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 X 5 mL). The combined organic layers were washed with H_2O (3 X 5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified via flash chromatography eluting with EtOAc/ H_2O (80:20) to afford 169 mg (43%) of desired product as a brown solid.

Example 41

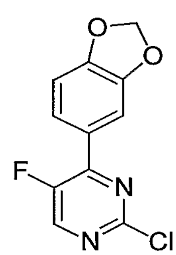
Preparation of *N*-(1,3-benzodioxol-5-yl)-*N*-[5-fluoro-2-(3-quinolinylamino)-4-pyrimidinyl]amine



To a suspension of (2Z)-1-(1,3-benzodioxol-5-yl)-3-(dimethylamino)-2-fluoro-2-propen-1-one obtained according to the process of Example 40 (51.0 mg, 0.215 mmol) and *N*-(3-quinolinyl)guanidine (64.0 mg, 0.215 mmol) in MeOH (2 mL) was added 0.5M NaOMe (1.29 mL, 0.645 mmol). This was heated to 70 °C and shaken for 36 h. Complete consumption of starting material was not obtained, but the reaction mixtures were concentrated in vacuo and purified via prep HPLC (RT 2.10 min, 10-90% CH_3CN/H_2O over 3.5 min) to afford 1.7 mg (1%) of the desired product as an off-white solid. ESIMS *m/z* 361.4 (MH^+).

Example 42

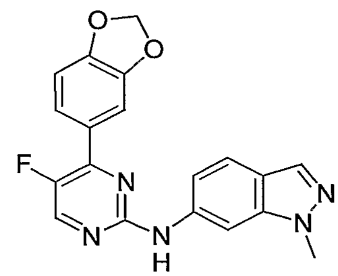
Preparation of 4-(1,3-benzodioxol-5-yl)-2-chloro-5-fluoropyrimidine intermediate



To a stirred solution of 1,3-benzodioxol-5-ylboronic acid (300 mg, 1.81 mmol), 2,4-dichloro-5-fluoro-pyrimidine (332 mg, 2.00 mmol) and sodium carbonate (384 mg, 3.62 mmol) in DME (10 mL) and H_2O (2 mL) was added $PdCl_2$(dppf) (30.0 mg, 0.04 mmol). After 0.5 h a precipitate began to form, and after 2 h the reaction was complete. The crude mixture was concentrated in vacuo and redissolved in H_2O. The resulting solid was filtered and dried to afford 443 mg (97%) of the desired product as a tan solid, mp 134-136 °C.

Example 43

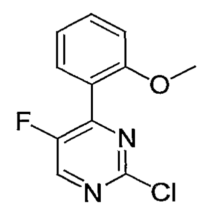
Preparation of *N*-[4-(1,3-benzodioxol-5-yl)-5-fluoro-2-pyrimidinyl]-1-methyl-1*H*-indazol-6-amine



To a suspension of 4-(1,3-benzodioxol-5-yl)-2-chloro-5-fluoropyrimidine obtained according to the process of Example 42 (75.0 mg, 0.297 mmol), and 5-amino-2-methylindazole in *n*-butanol (2 mL) was added 1N HCl (1 mL). This was warmed to 120 °C and shaken for 120 h. The crude reaction mixture was concentrated in vacuo and purified by prep HPLC (RT 2.89 min, 30-70% CH_3CN/H_2O over 3.5 min) to afford 2.2 mg (2%) of the desired product as a tan solid, mp 218-219 °C. ESIMS *m/z* 364.4 (MH^+).

Example 44

Preparation of 2-chloro-5-fluoro-4-(2-methoxyphenyl)pyrimidine intermediate

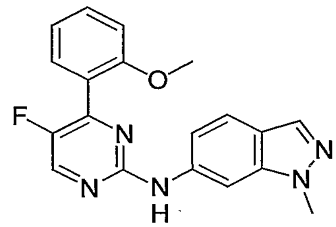


A suspension of 2,4-dichloro-5-fluoropyrimidine (3 mmol, 1 equiv) and $PdCl_2$dppf (0.06 mmol, 0.02 equiv) in 9 mL of deoxygenated DME was stirred for 5 min. 2-Methoxyphenylboronic acid (3.6 mmol, 1.2 equiv), sodium carbonate (6 mmol, 2 equiv), and 2 mL water were then added. The vial was capped under argon and shaken overnight. The reaction was diluted with ethyl acetate and water. The organic layer was separated, dried over sodium sulfate, filtered and

concentrated. The residue was purified by flash column chromatography (8% ethyl acetate in hexanes) to yield the desired product as a white solid. Total yield 45%.

Example 45

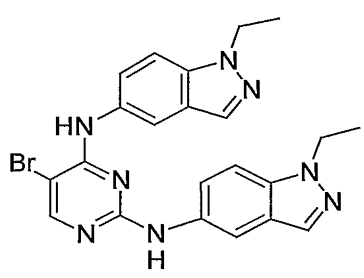
Preparation of *N*-[5-fluoro-4-(2-methoxyphenyl)-2-pyrimidinyl]-1-methyl-1*H*-indazol-6-amine



A suspension of 2-chloro-5-fluoro-4-(2-methoxyphenyl)pyrimidine according to the process of Example 44 (0.5 mmol, 1 equiv) and 1-methyl-6-amino-indazole (1 mmol, 2 equiv) in 2 mL of *n*-butanol and 1 mL of 1N HCl was shaken at 120 °C for 3 days. The reaction was concentrated and the resulting residue purified by HPLC. Fractions were combined, acetonitrile removed, and the resulting aqueous layer treated with saturated sodium bicarbonate solution to give a precipitate. This was filtered and dried in a vacuum oven overnight to yield the target compound as a pure compound. Total yield was 25%

Example 46

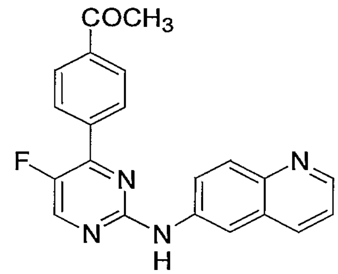
Preparation of *N*-{5-bromo-2-[(1-ethyl-1*H*-indazol-5-yl)amino]-4-pyrimidinyl}-*N*-(1-ethyl-1*H*-indazol-5-yl)amine



A solution of 5-bromo-2,4-dichloropyrimidine (100 mg, 0.20 mmol), 1-ethyl-1*H*-indazol-5-amine, and catalytic amount of hydrochloric acid in 1-butanol (3 mL) was heated at 115 °C overnight. Some yellow solid precipitated out. The solution was filtered. The filtrate was washed with a little bit of methanol and ethyl acetate to give a yellow solid (86.6 mg, 71.0%).

Example 47

Preparation of 1-{4-[5-fluoro-2-(6-quinolinylamino)-4-pyrimidinyl]phenyl}ethanone

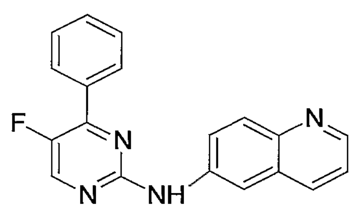


Step 1: 2,4-Dichloro-5-fluoropyrimidine (1 equiv) was allowed to react with 4-acetylphenylboronic acid (1.2 equiv), in the presence of $PdCl_2$dppf (0.06 equiv) and sodium carbonate (1.5-2 equiv), in DME and water (4:1 v/v) at rt to 60 °C for 2-6 h. The reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (EtOAc-hexane).

Step 2: The intermediate from Step 1 was treated with 6-aminoquinoline (2 equiv) in *n*-BuOH and 2N HCl (1:1 v/v) at 120 °C for 2-6 days. The solvents were removed by evaporation. The residue was purified by silica gel column (EtOAc-Hexane or MeOH-CH_2Cl_2) to give a pure solid product. LC-MS: RT 2.04 min; $[M+H]^+$ 359.

Example 48

Preparation of *N*-(5-fluoro-4-phenyl-2-pyrimidinyl)-6-quinolinamine

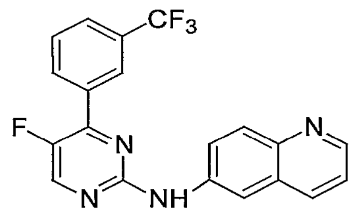


Step 1. 5-Fluoro-2,4-dichloropyrimidine (1 equiv) was allowed to react with phenylboronic acid (1.2 equiv) in the presence of $PdCl_2$dppf (0.02 equiv) and sodium bicarbonate (3 equiv), in DME and water (4:1 v/v) at 70 °C overnight. The reaction mixture was evaporated to dryness and the residue was purified by Biotage (15% EtOAc/Hexanes) to give the desired product (80% purity) that was used directly in the next step.

Step 2. The intermediate obtained in Step 1 was treated with 6-aminoquinoline (2 equiv) in *n*-BuOH/1N HCl (1/1) at 120 °C, or in 1N HCl at 100 °C for 10 days. It was cooled and neutralized with 2N Na_2CO_3, and extracted with *n*-BuOH. The organic layer was collected, and dried. The resulting crude product was purified by preparative TLC (60% EtOAc / hexanes). LC-MS: RT 2.08 min; $[M+H]^+$ 317.

Example 49

Preparation of *N*-{5-fluoro-4-[3-(trifluoromethyl)phenyl]-2-pyrimidinyl}-6-quinolinamine

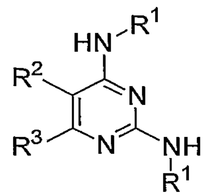


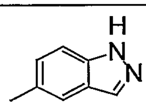
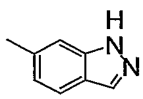
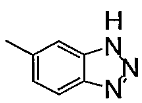
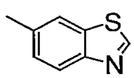
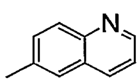
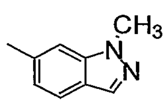
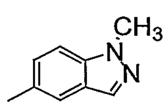
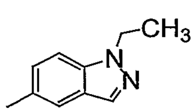
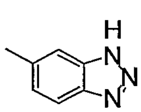
Step 1. To a solution of 2,4-dichloro-5-fluoropyrimidine (500 mg, 3.0 mmol) in degassed DME/H_2O (9.3 mL/1.8 mL) was added 3-trifluoromethyl phenylboronic acid (627 mg, 3.3 mmol), followed by $PdCl_2$(dppf) (49 mg, 0.060 mmol). The reaction was stirred at rt overnight. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (95:5 hexanes/EtOAc) to afford the desired product. The product was verified by ^{1}H NMR and LC/MS.

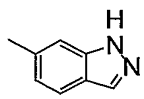
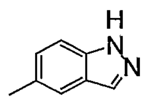
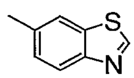
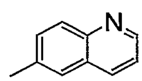
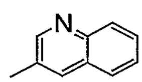
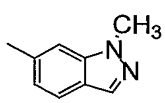
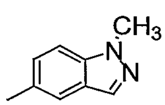
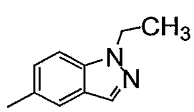
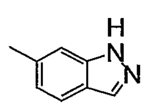
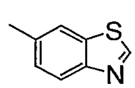
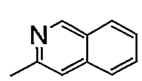
Step 2. To a solution of 2-chloro-5-fluoro-4-(3-trifluoromethyl phenyl)pyrimidine obtained in Step 1 (100 mg, 0.36 mmol) in *n*-BuOH (2 mL) were added an 6-amino quinoline (1 equiv) and 1N HCl (1 mL). The mixture was shaken at 125 °C over 4 days. The mixture was cooled to rt and concentrated under reduced pressure. The crude product was purified by preparative HPLC (C_{18} ODS, 10-90% CH_3CN/H_2O, 0.1%TFA) and dried in vacuo at 45 °C to afford the desired product in 12-17% yield. The product was verified by ^{1}H NMR and LC/MS: RT 2.73 min; $[M+H]^+$ 385.

Using methods analogous to the above described procedures, other examples of the invention were prepared and are listed in Tables 1-5 below:

Table1



Ex. No.	R^1	R^2	R^3	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
50		CF_3	H	2.00	411	4	
51		CF_3	H	2.13	411	4	
52		CF_3	H	2.01	413	4	
53		F	H	2.24	395	3	HCl salt
54		F	H	1.8	383	3	
55		F	H	1.64	388	2	
56		F	H	0.21	389	2	
57		F	H	2.02	417	4	
58		Br	H	0.32	423	2	

Ex. No.	R^1	R^2	R^3	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
59		Br	H	1.89	421	4	
60		Br	H	1.96	421	4	HCl salt
61		Br	H	2.26	455	2	
62		Br	H	1.6	441	2	
63		Br	H	2.15	443	2	
64		Br	H	1.93	449.5	2	
65		Br	H	1.53	449.5	2	
66		Br	H	2.2	478	4	
67		Cl	H	1.70	377	4	
68		H	H	1.49	377	2	
69		H	H	2.23	365	2	

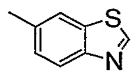
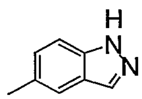
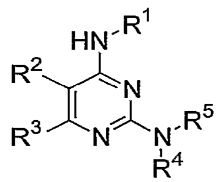
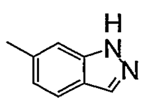
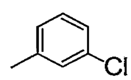
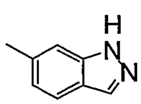
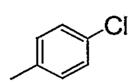
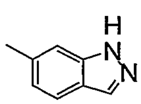
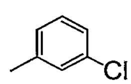
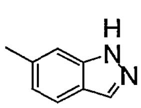
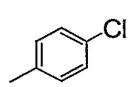
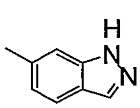
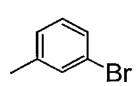
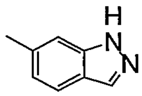
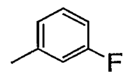
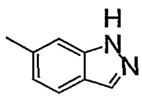
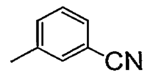
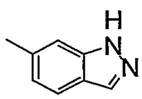
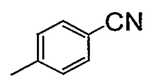
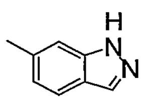
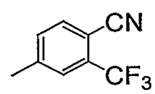
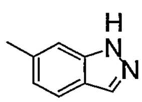
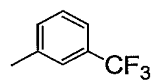
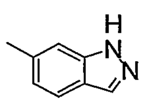
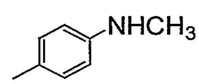
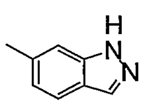
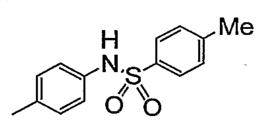
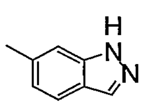
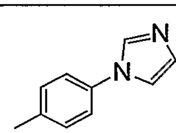
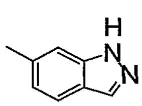
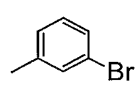
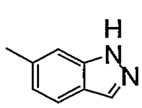
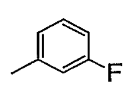
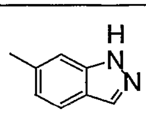
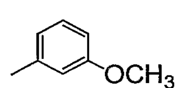
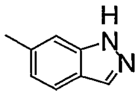
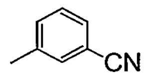
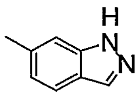
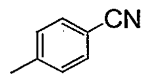
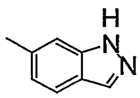
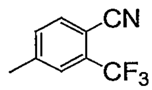
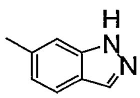
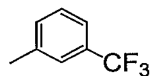
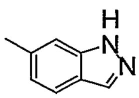
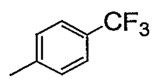
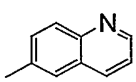
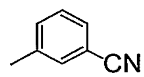
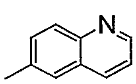
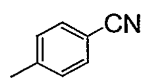
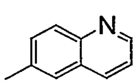
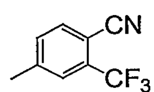
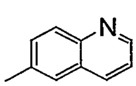
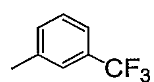
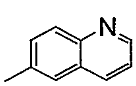
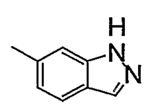
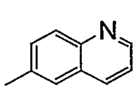
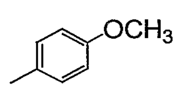
Ex. No.	R^1	R^2	R^3	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
70		CH_3	H	1.75	39	2	
71		CH_3	H	1.71	357	4	HCl salt

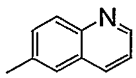
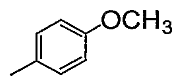
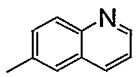
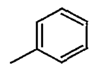
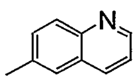
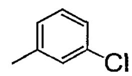
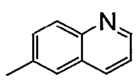
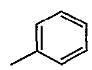
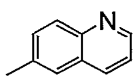
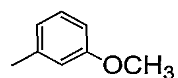
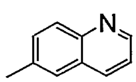
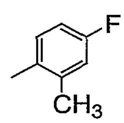
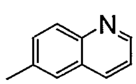
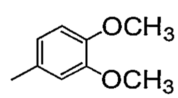
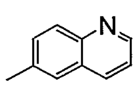
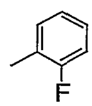
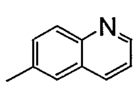
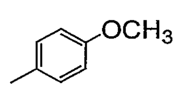
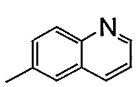
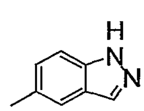
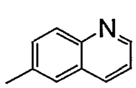
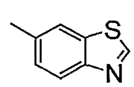
Table 2

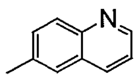
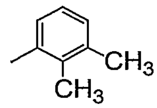
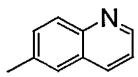
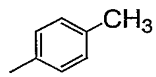
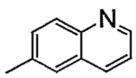
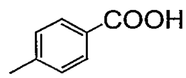
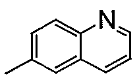
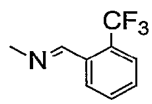
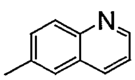
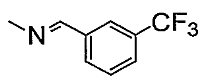
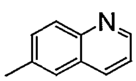
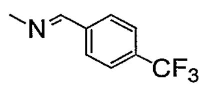
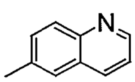
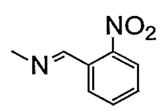
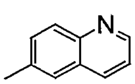
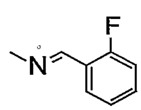
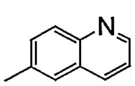
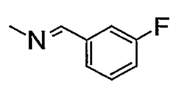
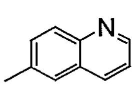
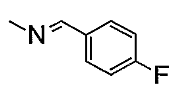
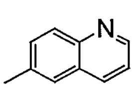
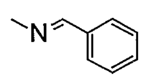


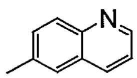
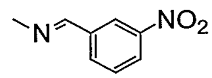
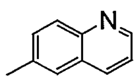
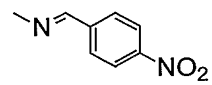
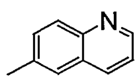
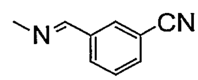
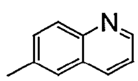
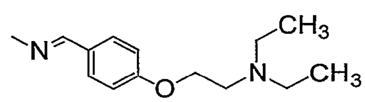
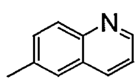
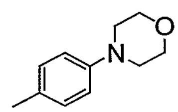
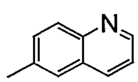
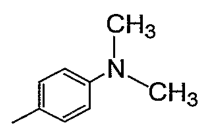
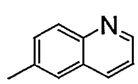
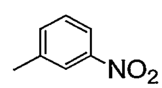
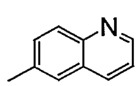
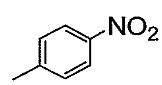
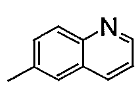
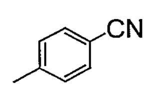
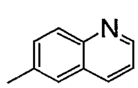
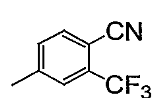
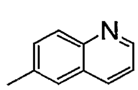
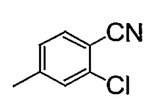
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Exam-ple
72		CH_3	H	H		2.07	351	7
73		CH_3	H	H		2.06	351	7
74		F	H	H		2.37	355	7
75		F	H	H		2.33	355	7
76		F	H	H		2.43	399	7

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
77		F	H	H		2.24	339	7
78		F	H	H		2.14	346	7
79		F	H	H		2.16	346	7
80		F	H	H		2.87	414	7
81		F	H	H		2.51	389	7
82		F	H	H		1.65	350	7
83		F	H	H		2.21	490	7
84		F	H	H		1.58	387	7
85		Cl	H	H		2.68	415	7
86		Cl	H	H		2.49	355	7
87		Cl	H	H		2.28	367	7

Ex. No.	R[1]	R[2]	R[3]	R[4]	R[5]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
88		Cl	H	H		2.46	362	7
89		Cl	H	H		2.62	362	7
90		Cl	H	H		3.13	430	7
91		Cl	H	H		2.76	405	7
92		Cl	H	H		2.87	405	7
93		F	H	H		2.13	357	7
94		F	H	H		2.25	357	7
95		F	H	H		2.48	425	7
96		F	H	H		2.31	400	7
97		F	H	H		2.04	372	15
98		F	H	CH_3		2.3	376	15

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
99		F	H	H		2.12	362	15
100		F	H	H		2.19	332	15
101		F	H	CH_3		2.59	380	15
102		F	H	CH_3		2.19	340	15
103		F	H	H		1.84	362	7
104		F	H	H		1.85	364	7
105		F	H	H		1.67	392	7
106		F	H	H		1.89	350	7
107		F	H	H		1.82	362	7
108		F	H	H		0.82	372	8
109		F	H	H		1.78	389	8

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
110		F	H	H		1.52	360	7
111		F	H	H		1.65	346	7
112		F	H	H		1.97	376	7
113		F	H	H		2.56	426	10
114		F	H	H		2.41	427	10
115		F	H	H		2.46	427	10
116		F	H	H		2.34	404	10
117		F	H	H		2.17	377.5	10
118		F	H	H		2.27	377.5	10
119		F	H	H		2.25	377.5	10
120		F	H	H		2.19	359.5	10

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
121		F	H	H		2.19	404.5	10
122		F	H	H		2.37	404.5	10
123		F	H	H		2.2	384.5	10
124		F	H	H		1.99	474.5	10
125		F	H	H		1.6	417	7
126		F	H	H		0.96	375.3	7
127		F	H	H		2.25	377.3	7
128		F	H	H		2.25	377.3	7
129		Br	H	H		2.27	417.5	7
130		Br	H	H		2.72	485	7
131		Br	H	H		2.56	451	7

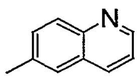
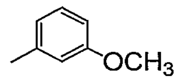
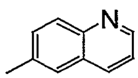
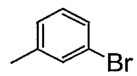
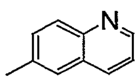
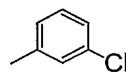
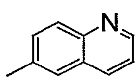
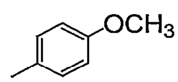
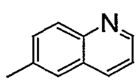
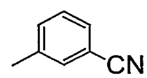
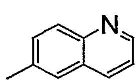
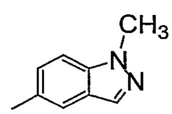
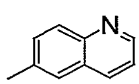
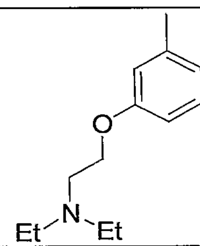
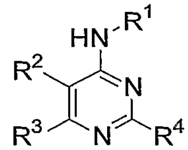
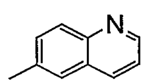
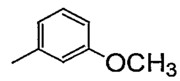
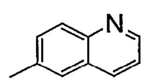
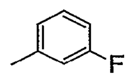
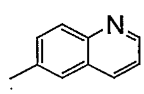
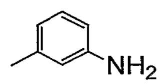
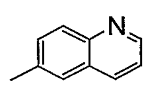
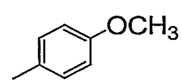
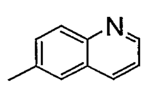
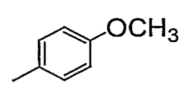
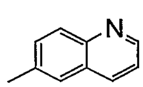
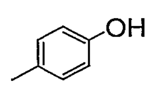
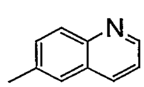
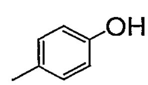
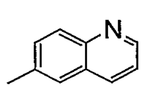
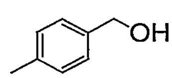
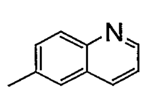
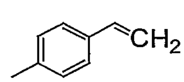
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example
132		Br	H	H		2.27	423	12
133		Br	H	H		2.52	471	12
134		Br	H	H		2.59	426	12
135		Br	H	H		2.3	422	12
136		Br	H	H		2.41	417	12
137		Br	H	H		1.64	446	15
138		CF_3	H	H		1.57	497	15

Table 3



Ex. No.	R^1	R^2	R^3	R^4	RT (min) LC-MS	Mass Spec. (ESI)M H+	Method of Example	Comments
139		CF_3	H		2.34	397	17	
140		CF_3	H		2.37	385	17	TFA salt
141		CF_3	H		1.53	382	17	TFA salt
142		CF_3	H		2.26	397	17	TFA salt
143		CF_3	H		2.22	397	17	Free Base
144		CF_3	H		1.93	383	17	TFA salt
145		CF_3	H		1.93	383	17	
146		CF_3	H		1.9	397	17	TFA salt
147		CF_3	H		2.56	393	17	

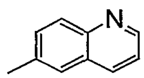
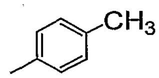
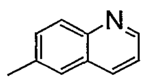
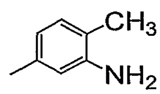
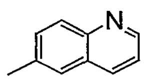
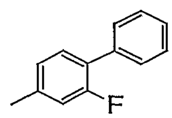
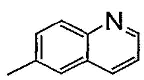
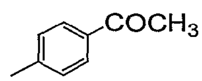
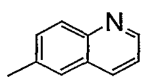
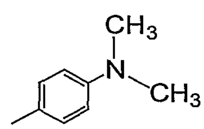
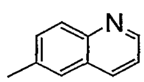
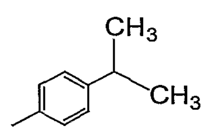
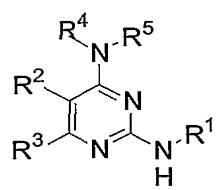
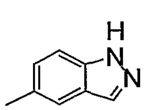
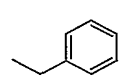
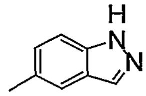
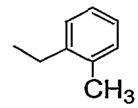
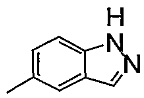
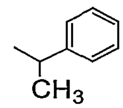
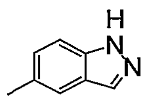
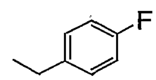
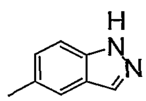
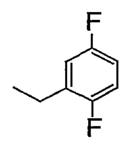
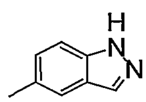
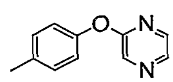
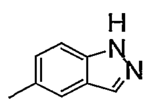
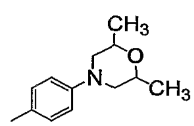
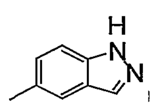
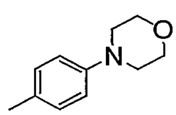
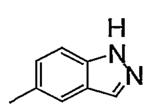
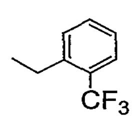
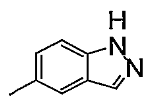
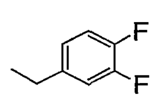
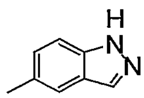
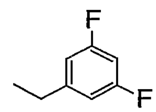
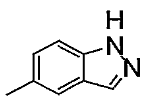
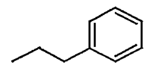
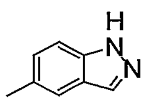
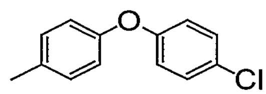
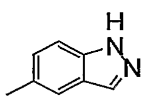
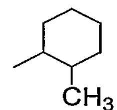
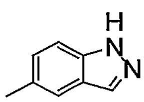
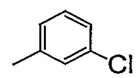
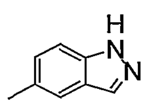
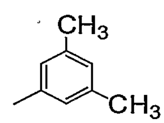
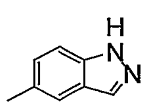
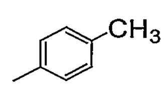
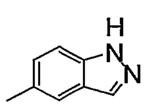
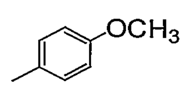
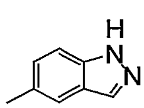
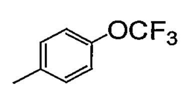
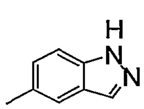
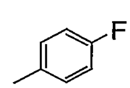
Ex. No.	R[1]	R[2]	R[3]	R[4]	RT (min) LC-MS	Mass Spec. (ESI)MH+	Method of Example	Comments
148		CF_3	H		2.45	381	17	
149		CF_3	H		1.86	396	17	
150		CF_3	H		2.67	461	17	
151		CF_3	H		2.22	409	17	
152		CF_3	H		2.37	410	17	
153		CF_3	H		2.52	409	17	

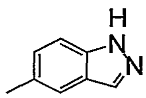
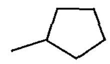
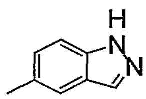
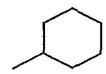
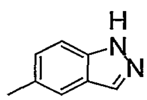
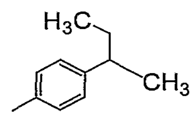
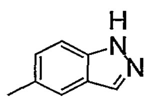
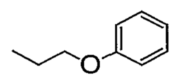
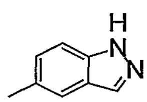
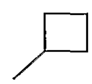
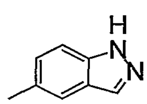
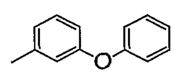
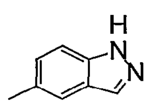
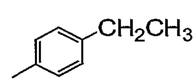
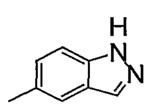
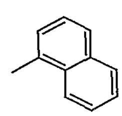
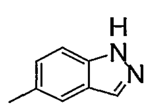
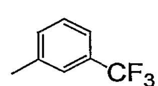
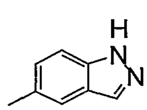
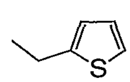
Table 4

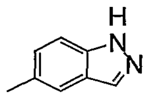
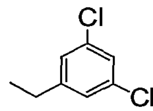
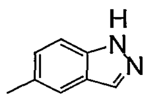
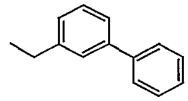
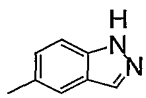
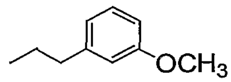
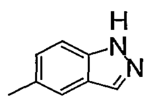
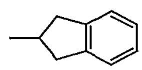
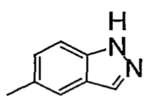
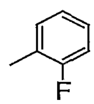
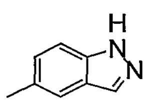
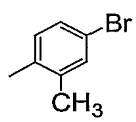
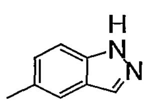
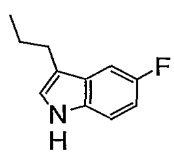
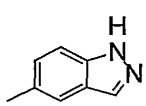
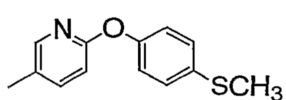
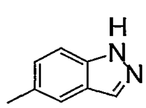
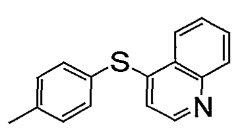


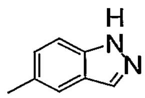
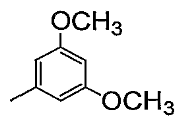
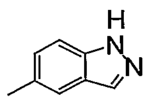
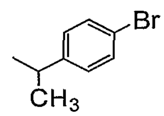
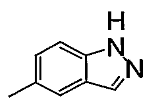
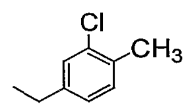
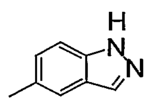
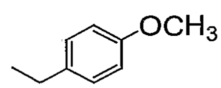
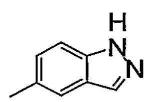
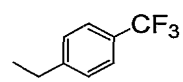
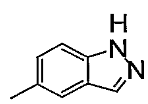
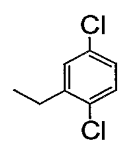
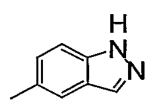
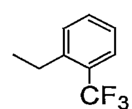
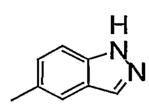
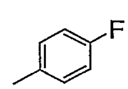
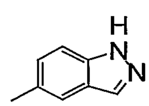
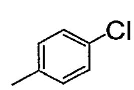
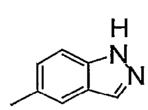
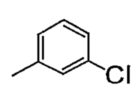
Ex. No.	R[1]	R[2]	R[3]	R[4]	R[5]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
154		Br	H	H		1.59	395	18	TFA salt

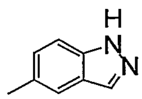
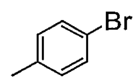
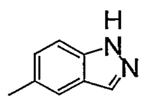
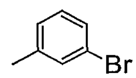
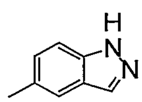
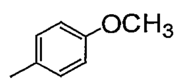
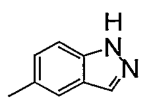
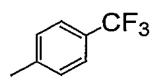
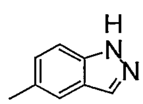
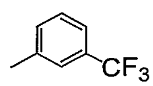
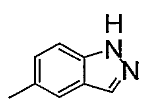
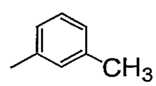
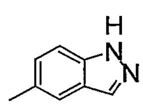
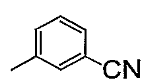
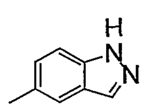
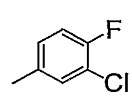
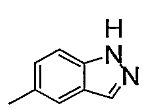
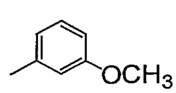
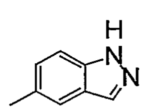
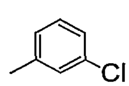
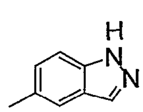
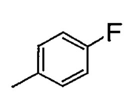
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Exam-ple	Com-ments
155		Br	H	H		1.77	409	18	TFA salt
156		Br	H	H		1.75	409	18	TFA salt
157		Br	H	H		1.62	413	18	TFA salt
158		Br	H	H		1.72	431	18	TFA salt
159		Br	H	H		1.88	475	18	TFA salt
160		Br	H	H		2.01	494	18	TFA salt
161		Br	H	H		1.68	466	18	TFA salt
162		Br	H	H		2.08	463	18	TFA salt
163		Br	H	H		1.88	431	18	TFA salt

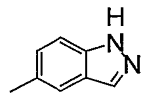
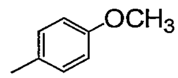
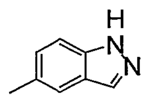
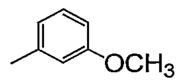
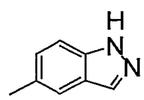
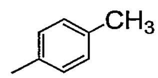
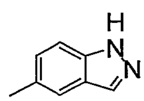
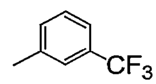
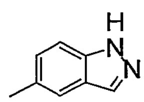
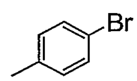
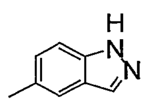
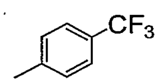
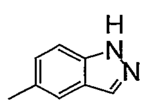
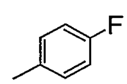
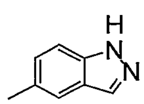
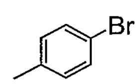
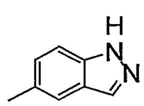
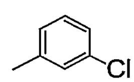
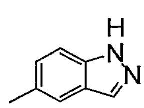
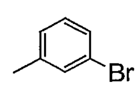
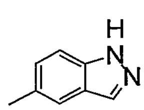
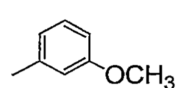
Ex. No.	R¹	R²	R³	R⁴	R⁵	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
164		Br	H	H		1.86	431	18	TFA salt
165		Br	H	H		1.89	409	18	TFA salt
166		Br	H	H		2.55	507	18	TFA salt
167		Br	H	H		2.13	401	18	TFA salt
168		Br	H	H		2.09	415	18	TFA salt
169		Br	H	H		2.23	409	18	TFA salt
170		Br	H	H		2.01	395	18	TFA salt
171		Br	H	H		1.75	425	18	TFA salt
172		Br	H	H		2.13	465	18	
173		Br	H	H		1.72	399	18	

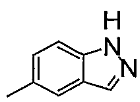
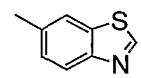
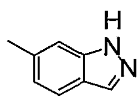
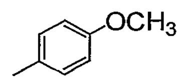
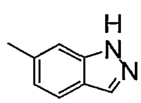
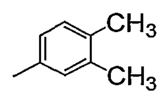
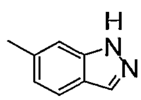
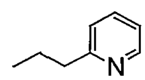
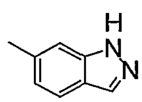
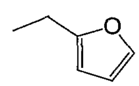
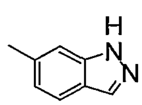
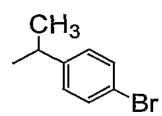
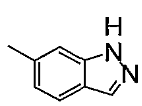
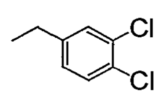
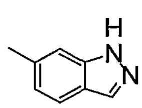
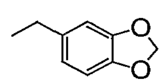
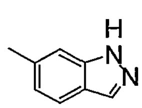
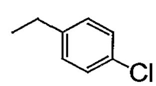
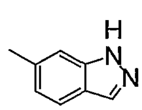
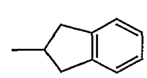
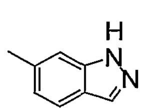
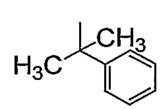
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
174		Br	H	H		1.87	373	18	
175		Br	H	H		2.00	387	18	
176		Br	H	H		2.26	437	18	
177		Br	H	H		1.94	425	18	
178		Br	H	H		1.61	359	18	TFA salt
179		Br	H	H		2.31	473	18	TFA salt
180		Br	H	H		2.08	409	18	
181		Br	H	H		2.00	431	18	TFA salt
182		Br	H	H		2.12	449	18	TFA salt
183		Br	H	H		1.76	401	18	TFA salt

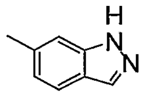
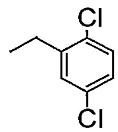
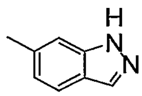
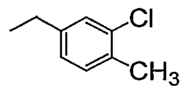
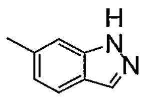
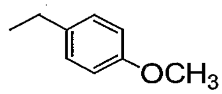
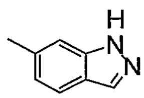
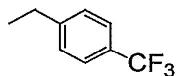
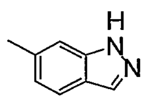
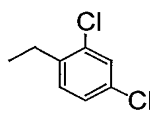
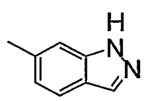
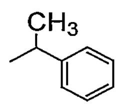
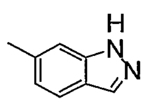
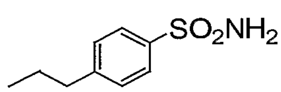
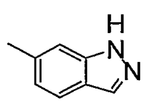
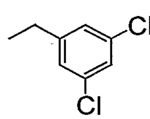
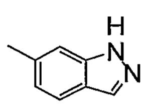
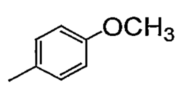
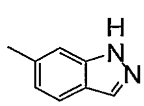
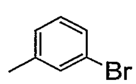
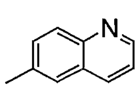
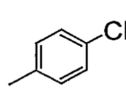
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
184		Br	H	H		2.15	463	18	TFA salt
185		Br	H	H		2.23	471	18	TFA salt
186		Br	H	H		1.97	439	18	TFA salt
187		Br	H	H		2.05	421	18	TFA salt
188		Br	H	H		1.72	473	18	TFA salt
189		Br	H	H		2.07	473	18	TFA salt
190		Br	H	H		2.08	466	18	TFA salt
191		Br	H	H		2.24	520	18	TFA salt
192		Br	H	H		1.83	540	18	TFA salt

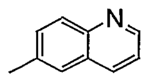
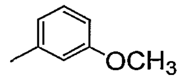
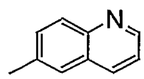
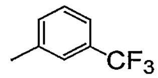
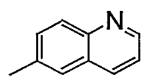
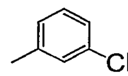
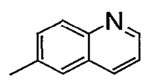
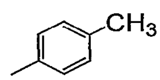
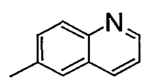
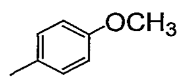
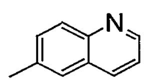
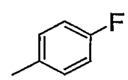
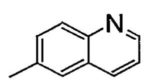
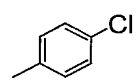
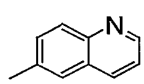
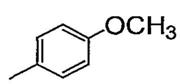
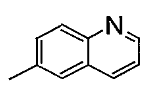
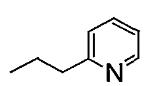
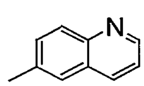
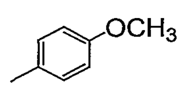
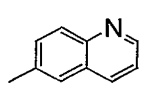
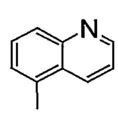
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
193		Br	H	H		1.89	441	18	TFA salt
194		Br	H	H		2.31	489	18	HCl salt
195		Br	H	H		2.34	459	18	HCl salt
196		Br	H	H		2.01	425	18	HCl salt
197		Br	H	H		2.30	463	18	HCl salt
198		Br	H	H		2.22	465	18	HCl salt
199		F	H	H		2.13	403	18	
200		F	H	H		1.78	340	18	
201		F	H	H		1.97	356	18	
202		F	H	H		1.93	356	18	

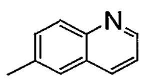
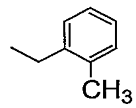
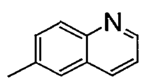
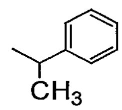
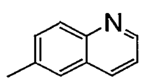
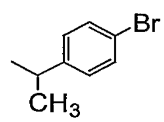
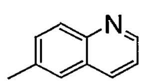
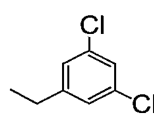
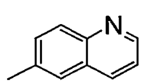
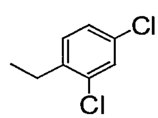
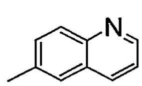
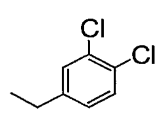
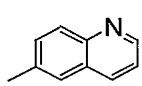
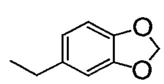
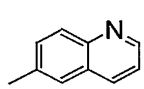
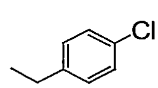
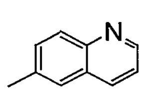
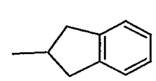
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
203		F	H	H		2.02	399	18	
204		F	H	H		1.97	399	18	
205		F	H	H		1.67	352	18	
206		F	H	H		2.13	390	18	
207		F	H	H		2.08	390	18	
208		F	H	H		1.89	336	18	
209		F	H	H		1.16	346	18	
210		F	H	H		2.04	373	18	
211		F	H	H		1.67	352	18	
212		F	H	CH_3		2.01	369	18	
213		Cl	H	H		2.24	355	18	

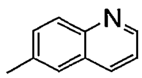
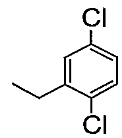
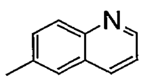
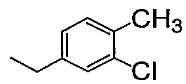
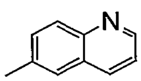
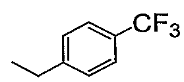
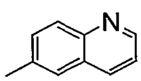
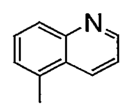
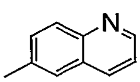
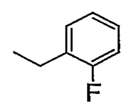
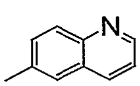
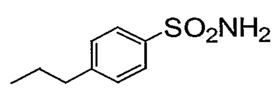
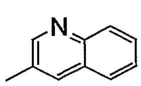
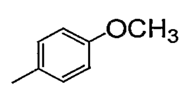
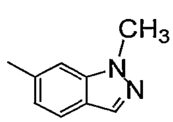
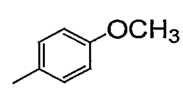
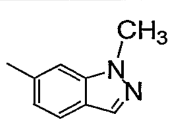
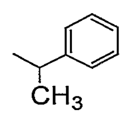
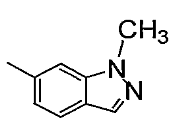
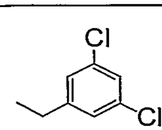
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
214		Cl	H	H		2.48	367	18	
215		Cl	H	H		2.35	367	18	
216		Cl	H	H		1.94	351	18	
217		Cl	H	H		2.18	405	18	
218		Cl	H	H		1.97	415	18	
219		Cl	H	H		2.21	405	18	
220		H	CH_3	H		1.55	335	18	
221		H	CH_3	H		1.97	395	18	
222		H	CH_3	H		1.86	351	18	
223		H	CH_3	H		1.88	395	18	
224		H	CH_3	H		1.72	347	18	

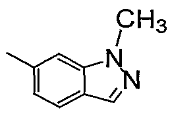
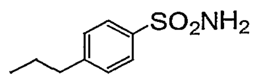
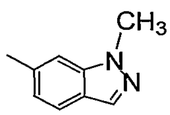
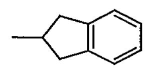
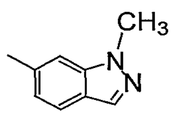
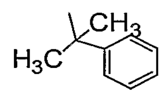
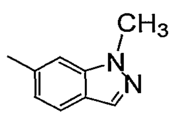
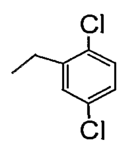
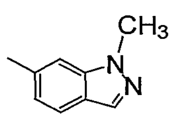
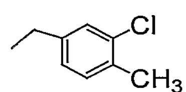
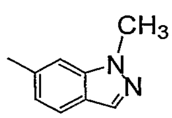
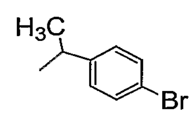
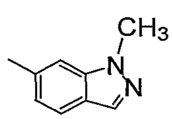
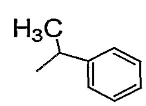
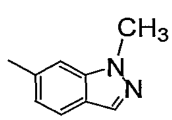
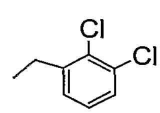
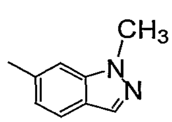
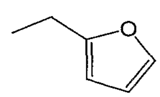
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
225		H	CH_3	H		1.80	374	18	
226		F	H	H		1.97	351	18	
227		F	H	H		2.18	349	18	
228		F	H	H		0.19	350	18	
229		Br	H	H		1.95	384	18	
230		Br	H	H		2.45	486	18	HCl salt
231		Br	H	H		3.12	466	18	
232		Br	H	H		2.14	4.39	18	
233		Br	H	H		2.29	431	18	
234		Br	H	H		2.34	421	18	TFA salt
235		Br	H	H		2.33	423	18	TFA salt

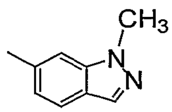
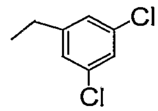
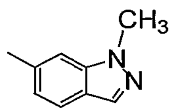
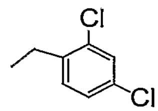
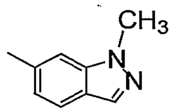
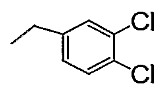
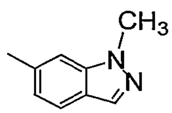
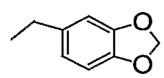
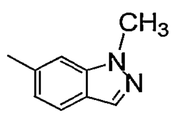
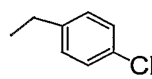
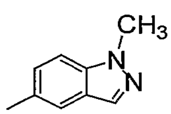
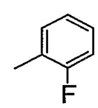
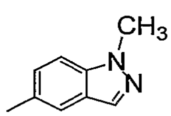
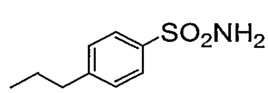
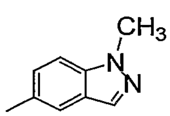
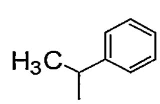
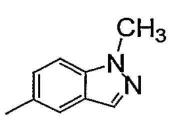
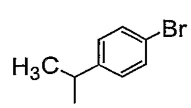
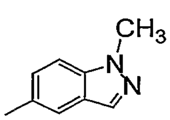
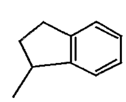
Ex. No.	R[1]	R[2]	R[3]	R[4]	R[5]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
236		Br	H	H		2.40	465	18	TFA salt
237		Br	H	H		2.36	445	18	
238		Br	H	H		2.16	425	18	HCl salt
239		Br	H	H		2.41	463	18	HCl salt
240		Br	H	H		3.19	465	18	
241		Br	H	H		2.29	407	18	
242		Br	H	H		1.92	489	18	
243		CF3	H	H		2.50	454	18	
244		H	CH_3	H		1.76	347	18	
245		H	CH_3	H		1.99	395	18	
246		Cl	H	H		2.09	382	18	

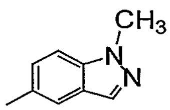
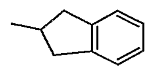
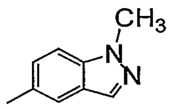
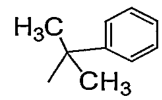
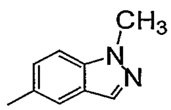
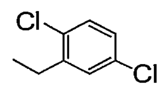
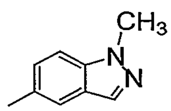
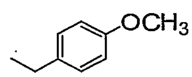
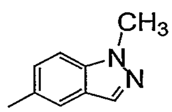
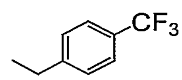
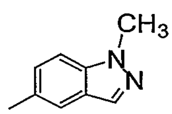
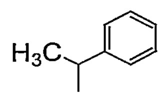
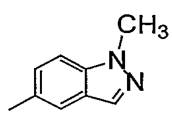
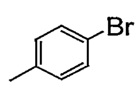
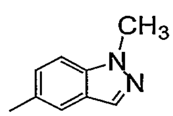
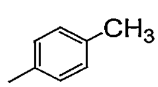
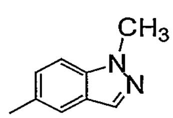
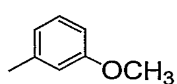
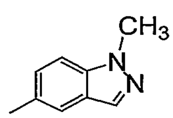
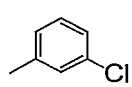
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
247		Cl	H	H		1.80	378	18	
248		Cl	H	H		2.33	416	18	
249		Cl	H	H		2.14	382	18	
250		Cl	H	H		2.11	362	18	
251		Cl	H	H		1.88	378	18	
252		F	H	H		1.70	350	18	
253		F	H	H		1.89	366	18	
254		F	H	H		1.94	362	18	
255		F	H	H		0.18	361	18	
256		CF_3	H	H		2.21	412	18	
257		CF3	H	H		1.76	433	18	

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
258		Br	H	H		2.78	420	18	
259		Br	H	H		2.18	419	18	Bis TFA salt
260		Br	H	H		2.45	497	18	
261		Br	H	H		2.36	476	18	
262		Br	H	H		3.01	476	18	
263		Br	H	H		3.31	479	18	
264		Br	H	H		1.74	450	18	
265		Br	H	H		2.16	440	18	
266		Br	H	H		2.25	433	18	

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
267		Br	H	H		2.27	476	18	HCl salt
268		Br	H	H		2.36	456	18	
269		Br	H	H		1.94	436	18	Bis TFA salt
270		Br	H	H		1.08	445	18	
271		Br	H	H		2.86	411	18	
272		Br	H	H		1.66	500	18	
273		F	H	H		2.19	362	18	
274		Cl	H	H		2.01	381	18	
275		F	H	H		2.19	362	18	HCl salt
276		CF_3	H	H		2.98	468	18	HCl salt

Ex. No.	R[1]	R[2]	R[3]	R[4]	R[5]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
277		Br	H	H		1.95	503	18	
278		Br	H	H		3.25	435	18	HCl salt
279		Br	H	H		2.49	437	18	HCl salt
280		Br	H	H		2.72	479	18	HCl salt
281		Br	H	H		2.53	459	18	HCl salt
282		Br	H	H		2.72	500	18	
283		Br	H	H		2.48	422	18	
284		Br	H	H		2.73	476	18	
285		Br	H	H		2.22	398	18	

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
286		Br	H	H		2.70	479	18	
287		Br	H	H		3.39	479	18	
288		Br	H	H		3.01	476	18	
289		Br	H	H		2.28	453	18	
290		Br	H	H		2.48	445	18	
291		Br	H	H		3.04	413	18	
292		Br	H	H		1.88	503	18	
293		Br	H	H		2.30	422	18	
294		Br	H	H		2.47	503	18	HCl salt
295		Br	H	H		2.36	437	18	HCl salt

Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
296		Br	H	H		3.06	435	18	HCl salt
297		Br	H	H		2.34	437	18	HCl salt
298		Br	H	H		2.52	465	18	HCl salt
299		Br	H	H		2.19	439	18	HCl salt
300		Br	H	H		2.46	477	18	HCl salt
301		F	H	H		2.13	362	18	Bis HCl salt
302		Cl	H	H		2.22	429	18	
303		Cl	H	H		2.03	365	18	
304		Cl	H	H		1.93	381	18	
305		Cl	H	H		2.21	385	18	

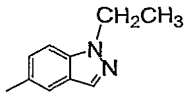
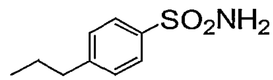
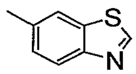
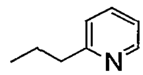
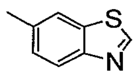
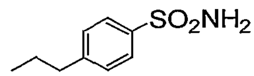
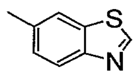
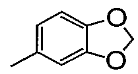
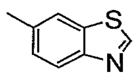
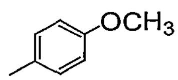
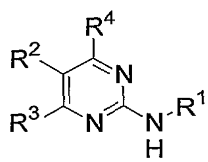
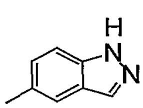
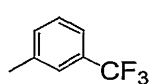
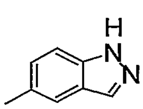
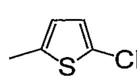
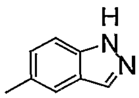
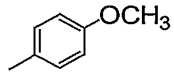
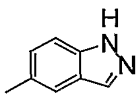
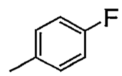
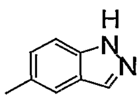
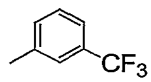
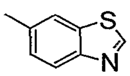
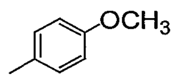
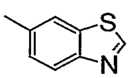
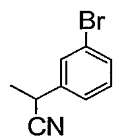
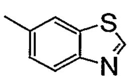
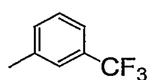
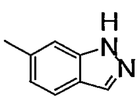
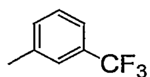
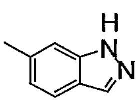
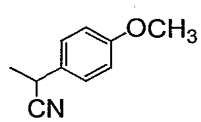
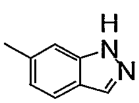
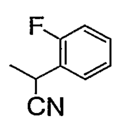
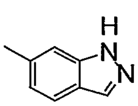
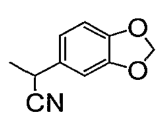
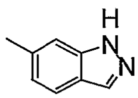
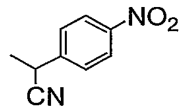
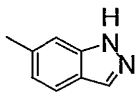
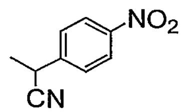
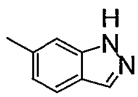
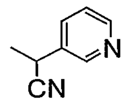
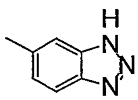
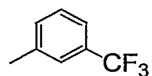
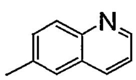
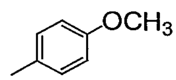
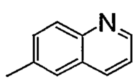
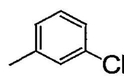
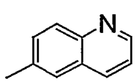
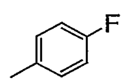
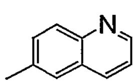
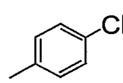
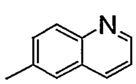
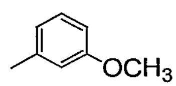
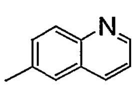
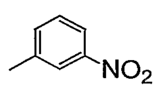
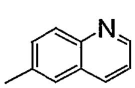
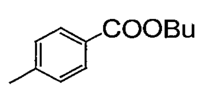
Ex. No.	R^1	R^2	R^3	R^4	R^5	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
306		Br	H	H		1.98	517	18	
307		F	H	H		0.19	367	18	
308		F	H	H		1.92	445	18	
309		H	CH_3	H		1.75	378	18	
310		H	CH_3	H		1.80	364	18	

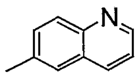
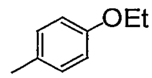
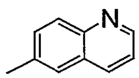
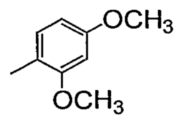
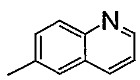
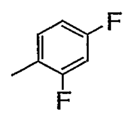
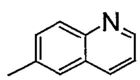
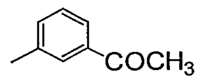
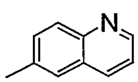
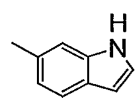
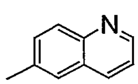
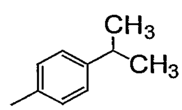
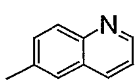
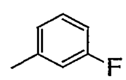
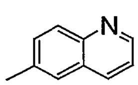
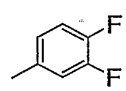
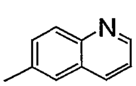
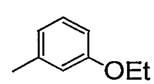
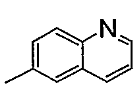
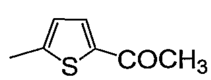
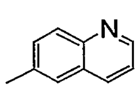
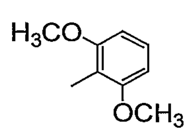
Table 5

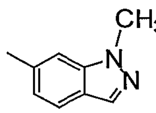
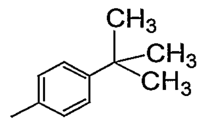
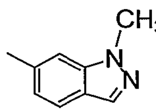
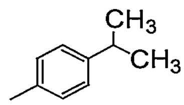
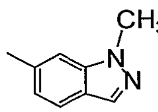
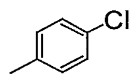
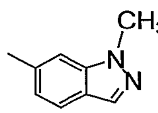
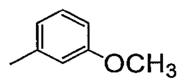
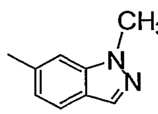
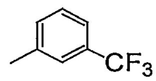
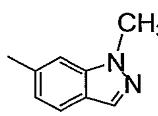
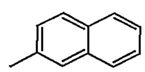
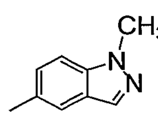
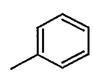
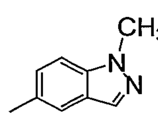
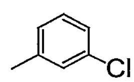
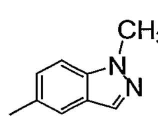
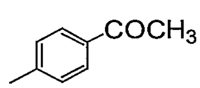
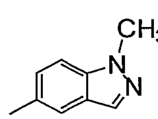
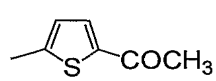


Ex. No.	R^1	R^2	R^3	R^4	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Method of Example	Comments
311		H	H		2.92	356	27	
312		CH_3	H		2.37	341	27	

Ex. No.	R^1	R^2	R^3	R^4	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
313		F	H		2.9	336	27	
314		H	CH_3		2.13	320	27	
315		H	CH_3		2.81	370	27	
316		F	H		3.22	353	27	
317		F	H		3.21	440	33	
318		H	H		3.34	373	27	
319		H	H		3.04	356	27	
320		F	H		2.85	375	33	
321		F	H		2.70	363	33	
322		Br	H		2.87	450	33	

Ex. No.	R^1	R^2	R^3	R^4	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
323		Br	H		2.92	450	33	
324		Br	H		2.92	450	33	TFA salt
325		Br	H		2.16	406	33	TFA salt
326		H	H		2.87	357	27	
327		F	H		2.48	347	27	
328		F	H		2.23	351	27	
329		F	H		2.21	335	27	
330		F	H		2.42	351	27	
331		F	H		2.12	347	27	
332		F	H		2.49	362	27	
333		F	H		3.52	417	34	

Ex. No.	R^1	R^2	R^3	R^4	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
334		F	H		3.23	361	34	
335		F	H		3.02	377	34	
336		F	H		2.39	353	34	
337		F	H		2.14	359	34	
338		F	H		2.21	356	34	
339		F	H		2.43	359	34	
340		F	H		2.09	335	34	
341		F	H		2.23	353	34	
342		F	H		2.24	361	34	
343		F	H		1.95	365	34	
344		F	H		2.10	377	34	

Ex. No.	R^1	R^2	R^3	R^4	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
355		F	H		3.48	376	34	
356		F	H		3.38	362	34	
357		F	H		3.21	354	34	
358		F	H		2.92	350	34	
359		F	H		3.62	388	34	
360		Cl	H		3.33	386	34	
361		F	H		2.65	320	34	
362		F	H		3.11	354	34	
363		F	H		2.78	362	34	
364		F	H		2.72	368	34	

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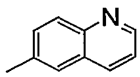
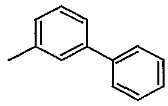
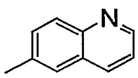
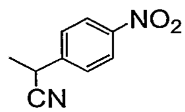
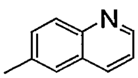
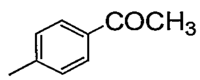
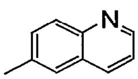
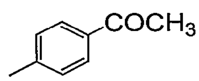
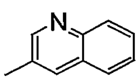
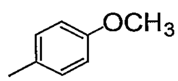
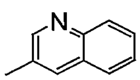
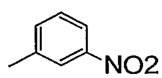
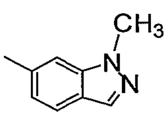
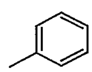
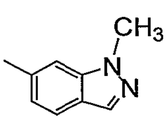
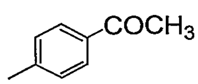
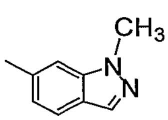
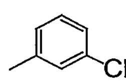
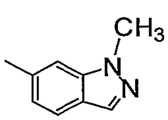
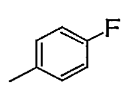
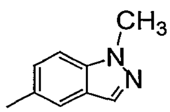
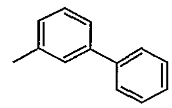
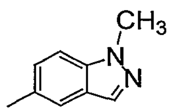
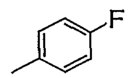
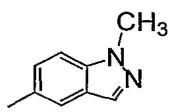
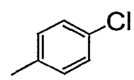
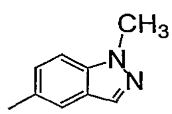
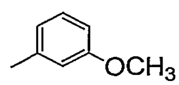
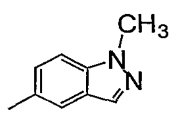
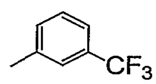
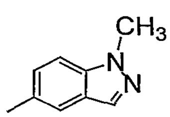
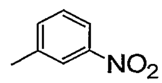
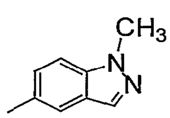
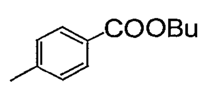
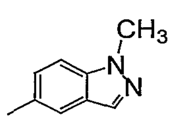
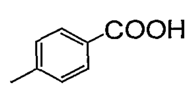
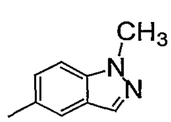
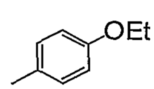
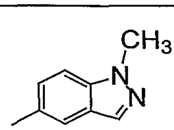
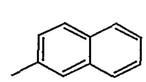
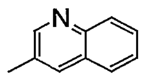
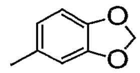
345		F	H		2.57	393	34	
346		Br	H		2.30	461	33	TFA salt
347		CF_3	H		2.15	409	34	
348		Cl	H		2.04	375	34	
349		F	H		2.71	347	34	
350		F	H		3.00	362	34	
351		F	H		2.92	320	34	
352		F	H		2.74	362	34	
353		F	H		3.18	354	34	
354		F	H		3.00	338	34	

Ex. No.	R[1]	R[2]	R[3]	R[4]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
365		F	H		3.45	396	34	
366		F	H		2.9	338	48	
367		F	H		3.23	354	48	
368		F	H		2.96	350	47	
369		F	H		3.57	388	49	
370		F	H		3.31	365	49	
371		F	H		3.73	420	34	
372		F	H		2.73	364	35	
373		F	H		4.00	364	34	
374		Cl	H		3.29	386	47	

Ex. No.	R[1]	R[2]	R[3]	R[4]	RT (min) (from LC-MS)	Mass Spec. (ESI) MH+	Meth-od of Exam-ple	Com-ments
375		F	H		2.10	361	41	

Biological tests

Elk-1 Assay:

The following assay measures the inhibitory activity of the compounds on Elk-1 transactivated luciferase expression. Elk-1 is a gene regulatory protein that is activated by MAP kinases (mitogen activated protein kinases). In this assay, epidermal growth factor (EGF) stimulates Elk-1 transactivation of luciferase expression through phosphorylation of the Gal4 (a yeast gene activator protein)-Elk-1 fusion protein (Hexdall and Zheng, 2001, Boulikas 1995). Hela Elk-1 luc cells are plated at 2 x 10^4 cells per well in 96-well plates in complete medium (DMEM, 10% FBS, 20 mM HEPES, 100 U/mL penicillin, 100 μg/mL streptomycin, 250 μg/ml G418 (geneticin) and 100 μg/ml hygromycin B; all reagents Gibco BRL). The cells are incubated at 37 °C in 5% CO_2 in a humidified incubator overnight. The cells are washed and subsequently incubated in serum-free medium containing 1% fatty acid free bovine serum albumin (BSA) for an additional 24 hours. Test compounds are added in serum-free medium and the plates are incubated for 45 min followed by addition of 100 ng/ml recombinant EGF or 50 ng/ml PMA (phorbol 12-myristate 13-acetate, Sigma). After a 5 h incubation period, luciferase activity is quantified in a Wallace Luminometer.

In vitro Proliferation Inhibition Assay:

HCT 116 human colorectal carcinoma cells (ATCC CCL247) were cultured in standard growth medium (DMEM, 10% FBS, 10 mM HEPES, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin) at 37 °C in 5% CO_2 in a humidified incubator. Cells were detached using trypsin and plated at a density of 3000 cells per well in 100 μL growth medium in a 96 well culture dish. Twenty-four hours

after plating, compounds were added and the cell number is quantified 72 h after treatment using a MTS assay (e.g. Promega CellTiter 96 Aqueous One Solution Cell Proliferation Assay #G3581. Briefly, the MTS assay is a colorimetric method for determining the number of viable cells in the proliferation assay. The MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)2-(4-sulfophenyl)-2H-tetrazolium) reagent is bioreduced by cells into a colored formazan product that is soluble in tissue cultured medium. The quantity of formazan product as measured by the amount of 490 nm absorbance is directly proportional to the number of living cells in culture.)

Test compounds were dissolved in 100% DMSO (dimethylsulfoxide) to prepare 10 mM stocks. Stocks were further diluted 1:250 in growth medium to yield working stocks of 40 μM test compound in 0.4% DMSO. Test compounds were serially diluted in a 6 point dose response from 10 μM to 0.033 μM in growth medium containing 0.4% DMSO to maintain constant DMSO concentrations for all wells. One hundred microliters of diluted test compound were added to each culture well to give a final volume of 200 μL). The treated cells were incubated for 72h at 37 °C. After the completion of the 72h incubation, 40 μL of MTS reagent is added to each well. The plates were incubated for 30min at 37°C and read at 490 nm.

In addition, the IC_{50} values were determined with a least squares analysis program using compound concentration versus percent inhibition.

% Inhibition = $[1-(T_{72h}\text{ test}-T_{0h})/(T_{72h}\text{ ctrl}-T_{0h})] \times 100$

where

T_{72h} test = LDH activity at 72 h in presence of test compound

T_{72h} ctrl = LDH activity at 72 h in absence of test compound

T_{0h} = LDH activity at Time Zero

Representative results are shown in Table 8 below:

Table 8.

Example No.	IC_{50} (μM)
1	0.48
10	3.56

Example No.	IC_{50} (μM)
56	0.36
57	0.60
66	0.4
74	0.4
373	0.88
390	0.24

A suitable assay for assessing inhibition of colony formation is as follows. HCT116 or H460 (ATCC #HTB177) cells are mixed with an agar-medium 1 x DMEM (DMEM powder, Gibco) + 1x FBS at a ratio 3:2; i.e. 3 mL agar (SeaPlaque agarose, FMC Corporation) + 2 mL cells. The initial cell concentration is 5000 cells/mL (resulting in 100 cells/well). 50 μL is plated as a bottom layer agar mix consisting of 6.3 mL 4x agar, 6.3 mL 2x DMEM, and 12.5 mL 1x DMEM + 2x FBS for a 0.6% f.c. 50 mL of regular growth medium (DMEM, 10% FBS, 10 mM HEPES, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin) and incubated at 37 °C in 5% CO_2 in a humidified incubator overnight. The compound (10mM stock in 100% DMSO) is added in serial dilutions ranging from 10 μM to 33nM the next day and the plates are incubated for another 7 days 37 °C in 5% CO_2 in a humidified incubator. MTS (Promega) analysis is performed essentially as described by the manufacturer. Briefly, 40 μL MTS are added to each well and the plates were incubated for 2 h at 37°C in 5% CO_2 in a humidified incubator, shaken for 1 min at room temperature, and read at 490 nm.

Detection of Apoptosis:

A suitable assay for determining apoptosis is as follows. H460 human lung cancer cells are plated in six well plates (Costar 3506) at 250,000 cells per well in standard medium (DMEM, 10% FBS, 10 mM HEPES, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin) and incubated over night at 37 °C in 5% CO_2 in a humidified incubator. The cells are treated with various concentrations of the test compounds for 24 h. Cells are harvested and fixed with 1% paraformaldehyde on ice for 15 min. Subsequently, the cells are rinsed and put in ice cold ethanol (80%) overnight at -20 °C. Apoptosis is detected using a TUNEL assay (Pharmingen, APO-BRDU kit) as described by the manufacturer. Briefly,

cells are incubated with DNA labeling solution for 1 h at 37 °C, washed and subsequently incubated with propidium iodide. In a dark room, the cells are Rnase treated. Samples were analyzed using a FACS Calibur (Becton Dickinson) using CellQuest software.

Using this assay, a representative compound of the present invention induced apoptosis.

In vivo Tumor Growth Inhibition Assay:

Inhibition of tumor growth in vivo is readily determined via the following assay: HCT 116, H460, or A549 cells are cultured as described above. The cells are harvested by trypsinization, washed, counted, adjusted to 2.5×10^7 cells/mL with ice cold phosphate-buffered saline (PBS), and subsequently stored on ice until transplantation. Xenograft experiments are conducted using eight-to-ten week-old female NCr nude mice (Taconic Labs) with an average body mass of about 20-25g. All the procedures are performed using sterile technique and in accordance with IACUC guidelines. Approximately 5×10^6 cells in a total volume of 0.2 mL PBS are injected subcutaneously in the flank region. Tumor measurements are performed one week after transplantation. Tumor weights are calculated using the formula (a x b x b)/2. Thereafter the mice are randomized and divided into several groups that reflect different dosages or schedules, respectively (n=10 mice/group). The test compounds are administered starting with day 8 after transplantation at various dosages (*e.g.* 0.75, 1.5, 3, 10, 30, and 100 mg/kg) and different schedules (*e.g.* twice a day (bid) for 14 days, once a day for fourteen consecutive days, or every other day for seven treatments in total). A suitable vehicle for oral administration is Cremophor, ethanol and 0.9% saline (12.5:12.5:75). Tumor measurements are performed twice per week. Tumor weights are calculated as described above. Student's T - test is used to verify the significance of the activity compared to untreated (vehicle only) controls. Animals are sacrificed after treatment and plasma was harvested for pharmacokinetic analyses. Tumors undergo further subsequent analyses, e.g. histology.

Representative compound of Example 59 demonstrated antitumor activity in this assay using HCT 116 and H460 cells.

Pharmaceutical Compositions:

Useful pharmaceutical dosage forms for administration of the compounds according to the present invention can be illustrated as follows:

Hard shell capsules:

A large number of unit hard shell capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules:

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets:

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium sterate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules:

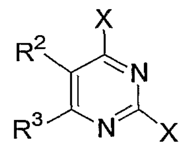
These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with

viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Additionally, the disclosure shows and describes only the preferred embodiments of the invention but, as mentioned above, it is to be understood that the invention is capable of use in various other combinations, modifications, and environments and is capable of changes or modifications within the scope of the inventive concept as expressed herein, commensurate with the above teachings and/or the skill or knowledge of the relevant art. The embodiments described hereinabove are further intended to explain best modes known of practicing the invention and to enable others skilled in the art to utilize the invention in such, or other, embodiments and with the various modifications required by the particular applications or uses of the invention. Accordingly, the description is not intended to limit the invention to the form disclosed herein. Also, it is intended that the appended claims be construed to include alternative embodiments.

What is claimed is:

1. A compound of the formula:



(I)

wherein

each X is independently NR^1R^6, NR^4R^5, or R^4, with the proviso that at least one X must be NR^1R^6;

each R^1 is independently an optionally substituted fused bicyclic unsaturated ring containing 9 or 10 atoms and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein said substitution on said ring is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, optionally substituted alkyl, and optionally substituted alkenyl wherein the substitution on said alkyl and alkenyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl;

R^2 is hydrogen, halo, optionally substituted alkyl, or an optionally substituted $-Y_{(n)}$-mono-ring group or $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, $-OR^8$, -C=O, $-NO_2$, $-CONR^8R^9$, and optionally substituted alkyl, wherein said substitution on each of said alkyls is independently selected from the group consisting of $-NR^8R^9$, $-OR^8$, and fluoro;

R^3 is hydrogen, alkyl, or halo;

each R^4 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O;

wherein n is 0 or 1, and Y is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl and -C(CN)-; wherein R^4 can also be hydrogen or alkyl when R^5 is present; and wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^5 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or an optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and $-N=CHCH_3$; and wherein said substitution on said ring group is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^6 is independently hydrogen or alkyl;

each R^8 and R^9 is independently hydrogen, optionally substituted C_1-C_5 alkyl, optionally substituted aryl, or optionally substituted arylalkyl, wherein said substitution is selected from the group consisting of optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of fluoro and dialkylamino;

and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 wherein:

each X individually is $-NR^1R^6$, $-NR^4R^5$, or R^4, with the proviso that at least one X is $-NR^1R^6$;

each R^1 is independently an optionally substituted moiety selected from the group consisting of indazolyl, quinolinyl, benzothiazolyl, benzotriazolyl, or benzoxazolyl, wherein said substitution is selected from the group consisting of hydrogen, methyl, and ethyl;

R^2 is halo or optionally substituted alkyl, wherein said substitution is selected from the group consisting of fluoro, $-COOR^8$, $-COOR^9$, and $-CONR^8R^9$;

R^3 is hydrogen or methyl;

each R^4 is hydrogen, methyl, phenyl, aryl, benzothiophenyl, pyridinyl, indolyl, naphthalenyl, biphenyl, indanyl, indenyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzotriazolyl, cyclohexanyl, cyclopentanyl, cyclobutanyl, or multiple rings which are linked covalently, either directly or via a linker, wherein said linker is selected from the group consisting of methylene, O, S, N, $-R^8-SO_2$, $-SO_2-NR^8$, $-NR^8CO-$ and $-CONR^8$;

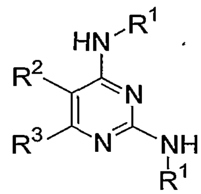
each R^5 is independently an optionally substituted $-Y_{(n)}$-mono-ring group or an optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and -N=$CHCH_3$; and wherein said substitution is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

each R^6 is independently hydrogen or alkyl;

each R^8 and R^9 is independently hydrogen, optionally substituted C_{1-5}-alkyl, optionally substituted aryl, and optionally substituted arylalkyl, wherein said substitution is selected from the group consisting of optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of fluoro and dialkylamino;

and pharmaceutically acceptable salts and prodrugs thereof.

3. A compound according to claim 1 of the formula



(I-1)

wherein

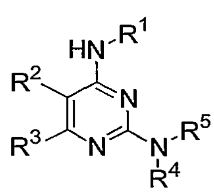
each R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, bromo, chloro, methyl, or trifluoromethyl; and

R^3 is hydrogen or methyl;

and pharmaceutically acceptable salts thereof.

4. A compound according to claim 1 of the formula:



(I-2)

wherein:

each R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, bromo, chloro, methyl, or trifluoromethyl;

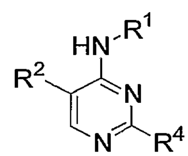
R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl; and

R^5 is an optionally substituted moiety selected from the group consisting of phenyl, pyridyl, thiophene, furan, $-Y_{(n)}$-mono-ring group or $-Y_{(n)}$-multi-ring group, said ring group in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n is 0 or 1, and -Y- is selected from the group consisting of straight or branched-chain C_{2-3}-alkylenyl, -N=CH, and $-N=CHCH_3$; and wherein said substitution is selected from the group consisting of halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, $-NO_2$, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R_9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl wherein said substitution on said alkyl is selected from the group consisting of $-NR^8R^9$, $-OR^8$, fluoro, methenyl, and ethenyl; with the proviso that the multi-ring group cannot be benzimidazolyl;

and pharmaceutically acceptable salts and prodrugs thereof.

5. A compound according to claim 1 of the formula:



(I-3)

wherein:

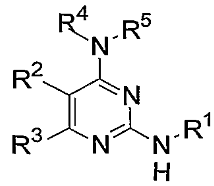
R^1 is 5-quinolyl or 6-quinolyl;

R^2 is fluoro or trifluoromethyl; and

R^4 is optionally substituted phenyl or pyridyl, wherein said substitution is selected from the group consisting of halo, amino, hydroxy, acetyl, alkyl, alkoxy, alkenyl, hydroxyalkyl, dialkylamino, and phenyl,

and pharmaceutically acceptable salts and prodrugs thereof.

6. A compound according to claim 1 of the formula



(I-4)

wherein:

R^1 is independently 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, chloro, bromo, methyl, or trifluoromethyl;

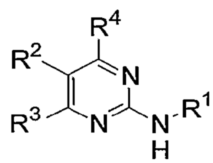
R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl; and

R^5 is an optionally substituted -Y(n)-moiety, wherein n is 0 or 1, Y is selected from the group consisting of straight- or branched-chain C_{2-3}-alkylenyl, -N=CH, and -N-$CHCH_3$, and said moiety is selected from the group consisting of cycloalkyl, phenyl, napthyl, pyridyl, thienyl, furyl, quinolinyl, benzothiophenyl, benzothiazolyl, indol-3-yl, and quinoline-4-thio, said substitution being selected from the group consisting of methyl, ethyl, fluoro, bromo, chloro, trifluoromethyl, methoxyl, methylenedioxyl, sulfonamidyl, morpholinyl, and -O-pyrazinyl;

and pharmaceutically acceptable salts and prodrugs thereof.

7. A compound according to claim 1 of the formula



(I-5)

wherein:

R^1 is 5-indazolyl, 6-indazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-quinolinyl, 5-(1-methyl)indazolyl, 6-(1-methyl)indazolyl, 5-(1-ethyl)indazolyl, 6-(1-ethyl)-indazolyl, 3-quinolyl, or 3-isoquinolyl;

R^2 is hydrogen, fluoro, methyl, bromo, chloro, trifluoromethyl, $-CO_2CH_3$, $-CO_2H$, and -CO-morpholinyl;

R^3 is hydrogen or methyl; and

R^4 is an optionally substituted $-Y_{(n)}$-mono-ring group or optionally substituted $-Y_{(n)}$-multi-ring group, said ring groups in each case containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from the group consisting of N, S, and O; wherein n = 0 or 1, -Y- is -C(CN)-, and wherein said ring group is selected from the group consisting of optionally substituted phenyl or pyridyl, wherein said substitution is selected from the group consisting of halo, amino, hydroxy, acetyl, -alkyl, alkoxy, alkenyl, hydroxyalkyl, dialkylamino, and phenyl;

and pharmaceutically acceptable salts and prodrugs thereof.

8. A compound according to claim 1 selected from the group consisting of the compounds of Examples 1 - 375.

9. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable adjuvant, buffer, or carrier.

10. A method for inhibiting kinases in a warm-blooded animal in need thereof by administering at least one of the compounds of the present invention in an amount sufficient to inhibit said kinase.

11. The present invention also relates to a method for treating a CDK-dependent disorder or disease in a warm-blooded animal in need of same, by administering to said animal at least one of the compounds of the present invention in an amount sufficient to inhibit CDK.

12. A method for inhibiting cellular proliferation in a warm-blooded animal in need thereof by administering to said animal at least one of the compounds of the present invention in an amount sufficient to inhibit said proliferation.

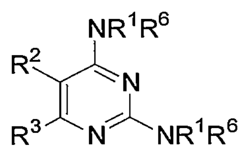
13. A method of inhibiting proliferative disorders in warm-blooded animals, comprising administering to said animal a compound of claim 1 in an amount sufficient to inhibit

14. A method of treating a warm-blooded animal suffering from cancer or neoplastic disease by administering to said warm-blooded animal an effective amount of at least one of the compounds of the present invention.

15. A method of treating a warm-blooded animal suffering from viral infection by administering to said warm-blooded animal an effective amount of at least one of the compounds of the present invention.

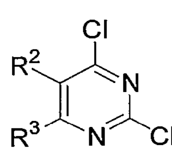
16. A method for modulating apoptosis in a warm-blooded animal in need thereof by administering at least one of the compounds of the present invention in an amount sufficient to modulate apoptosis.

17. A process for making compounds of the formula (Ia):



(Ia)

said process comprising reacting a compound of the formula (III):



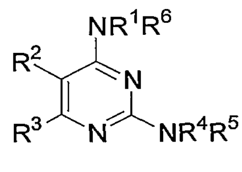
(III)

with an amine of the formula R^1R^6NH in a protic solvent to yield the compound of formula (Ia); wherein R^6 is hydrogen and R^1, R^2, and R^3 are as defined in claim 3.

18. The process of claim 17 wherein said reaction is carried out in the presence of an acid.

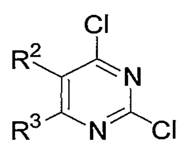
19. The process of claim 17 wherein said reaction is carried out in the presence of a base.

20. A process for making a compound of the formula (Ib):



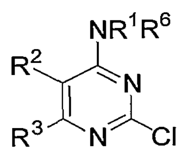
(Ib)

said process comprising reacting a compound of the formula (III)



(III)

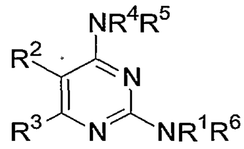
with an amine of the formula R^1R^6NH in a base to yield a compound of the formula (IV)



(IV)

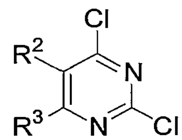
followed by reaction of the compound of formula (IV) with HNR^4R^5 to yield a compound of the formula (Ib), wherein R^6 is hydrogen and R^1, R^2, R^3, R^4, and R^5 are as defined in claim 4.

21. A process for making a compound of the formula (Ic)



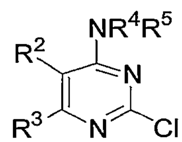
(Ic)

said process comprising reacting a compound of the formula (III)



(III)

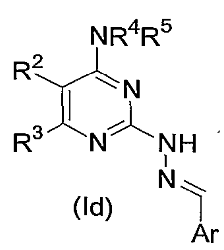
with an amine of the formula R^4R^5NH in the presence of base to give the compound of the formula (V)



(V)

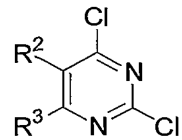
followed by reaction with a compound of formula (V) with HNR^1R^6 in acid to yield the compound of formula (Ic), wherein R^6 is hydrogen and R^1, R^2, R^3, R^4, and R^5 are as defined in claim 6.

22. A process for making a compound of the formula (Id):



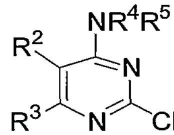
(Id)

said process comprising reacting a compound of the formula (III)



(III)

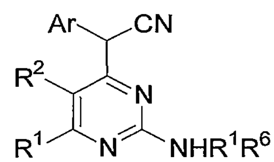
with an amine of the formula R4R5NH in base to give the compound of the formula (V):



(V)

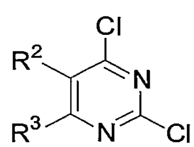
followed by reaction of the compound of formula (V) with hydrazine, followed by reaction with ArCHO to yield the compound of formula (Id), wherein R^2, R^3, R^4, and R^5 are as defined in claim 1.

23. A process for making a compound of formula (Ie):



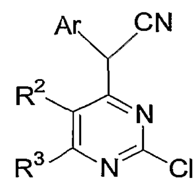
(Ie)

said process comprising reacting a compound of formula (III)



(III)

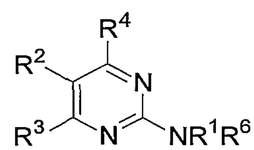
with a nitrile, represented by $ArCH_2CN$, where Ar is an aryl or heteroaryl radical, in the presence of a strong base, to provide the chloropyrimidine of formula (VIa):



(VIa)

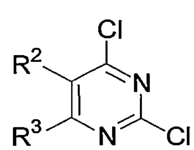
followed by reaction of the compound of formula (VIa) with an amine of formula R^1R^6NH to yield the compound of formula (Ie), wherein R^6 is hydrogen and R^1, R^2, and R^3 are as defined in claim 7.

24. A process for making a compound of formula (If):



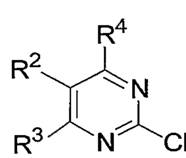
(If)

said process comprising reacting a compound of formula (III):



(III)

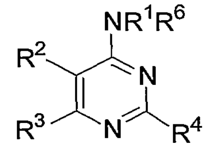
with a boronic acid of formula $R^4B(OH)_2$ in the presence of a palladium catalyst and a base to give a chloropyrimidine of formula (VIb)



(VIb)

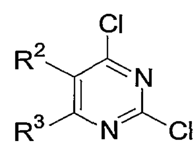
followed by reaction of the compound of formula (VIb) with an amine of the formula R^1R^6NH, to yield compounds of formula (If), wherein R^6 is hydrogen and R^1, R^2, R^3, and R^4 are as defined in claim 7.

25. A process for making a compound of formula (Ig)



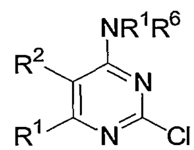
(Ig)

said process comprising reacting a compound of the formula (III)



(III)

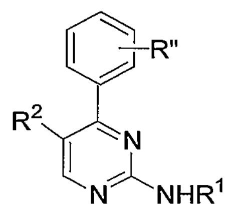
with a compound of the formula R^1R^6NH in a base to give the compound of formula (IV)



(IV)

followed by reaction of the compound of formula (IV) with a boronic acid of formula $R^4B(OH)_2$ in the presence of a palladium catalyst and a base to yield the compound of formula (Ig), wherein R^6 is hydrogen and R^1, R^2, R^3, and R^4 are as defined in claim 5.

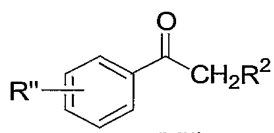
26. A process for making compounds of the formula (Ih)



(Ih)

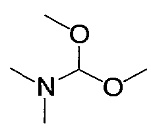
said process comprising the steps of

(a) reacting a compound of formula (VII)



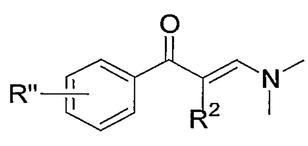
(VII)

with DMF-dimethylacetal of formula (VIII)



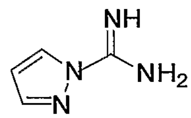
(VIII)

in a refluxing solvent to give an enaminone intermediate of formula (IX)



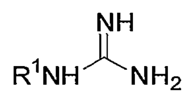
(IX)

(b) reacting a compound of formula (X)



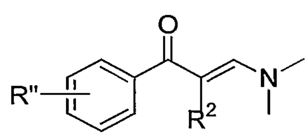
(X)

with an amine of the formula R^1NH_2 with heating in a higher boiling solvent to give the compound of formula (XII)



(XII)

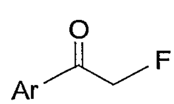
(c) reacting the enaminone of formula (IX)



(IX)

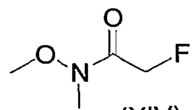
with the guanidine of formula (XII) in a protic solvent and a base to yield the compound of formula (Ih), wherein R" is methyl, methoxy, $-O-CH_2-$, fluoro, CN, or NO_2, and R^1 and R^2 are as defined in claim 1.

27. A process for making a compound of formula (XV)



(XV)

said process comprising reacting an aryl or heteroaryl bromide of the formula ArBr with butyllithium to form the aryllithium compound of the formula ArLi, followed be reaction of the compound of formula ArLi with a compound of the formula (XIV)



(XIV)

to yield the compound of formula (XV).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30616

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 A61P31/12 A61P35/00 C07D401/12 C07D403/12 C07D409/14 C07D405/14 C07D417/12 C07D401/14 C07D417/14 C07D403/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 22601 A (KAY DAVID ;BINCH HAYLEY (GB); GOLEC JULIAN (GB); KNEGTEL RONALD (G) 21 March 2002 (2002-03-21) claim 1; examples II-19,II-24,II-25,II-26,II-27	1,2, 8-16,25
X	WO 01 64654 A (BREAULT GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) claim 1	1-4,6, 8-22
X	WO 00 18761 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06) claims 1,2	1-26

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2002	21. 02. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 11095 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 19 March 1998 (1998-03-19) Claims 1, 4, 6, 9, examples, e.g. ex. 1, 2	1,2, 7-16,24, 26
X	WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) Claim 1, examples 101, 109	1,2,4, 8-16,20
X	WO 01 40215 A (PFIZER PROD INC ;BLUMENKOPF TODD ANDREW (US); MUELLER EILEEN ELLIO) 7 June 2001 (2001-06-07) claims 1,11,12,15	1,2,9,10
X	WERBEL ET AL.: "Synthesis and antimalarial effects of 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole and related benzimidazoles and 1H-imidazo[4,5-b]pyridines (1,2)" J. HETEROCYCL. CHEM., vol. 10, no. 3, 1973, page 363-382 XP009001685 table III	1,9

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			AU	9091401	A	26-03-2002
			AU	9094401	A	26-03-2002
			AU	9101301	A	26-03-2002
			AU	9267001	A	26-03-2002
			AU	9455801	A	26-03-2002
			AU	9687101	A	26-03-2002
			AU	9687501	A	26-03-2002
			WO	0222603	A1	21-03-2002
			WO	0222601	A1	21-03-2002
			WO	0222604	A1	21-03-2002
			WO	0222605	A1	21-03-2002
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			WO	0222602	A2	21-03-2002
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			AU	3404702	A	01-07-2002
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			WO	02059112	A2	01-08-2002
			WO	02068415	A1	06-09-2002
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			EP	0862560	A1	09-09-1998
			WO	9719065	A1	29-05-1997
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INTERNATIONAL SEARCH REPORT

ɪrmation on patent family members

International Application No
PC.,.S 02/30616

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9719065	A		US	5958935 A	28-09-1999
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			EP	1242403 A1	25-09-2002
			WO	0140215 A1	07-06-2001
			NO	20022557 A	29-05-2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/30616

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1(part), 2(part), 4-8(part),10-12 (part),14-16 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-26

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Claims Nos.: 1(part), 2(part), 4-8(part),10-12 (part),14-16 (part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Even the dependent claims are anticipated by many of the cited documents. The documents cited in the International Search Report are merely a representative selection of the relevant documents found.

In the definition of R2 in claim 1, Y and n are not defined. There is no further information concerning these groups in the description. Furthermore, the Y groups defined for R4 and R5 differ from one another, hence the Y groups which are defined in claim 1 cannot be assumed to also apply to R2 (as it would not be clear whether to take those of R4 or those of R5). For this reason, claim 1 has only been searched insofar as R2 is H, halo, substituted alkyl, CO2H, CO2CH3 or CO-morpholinyl, i.e. definitions which are clearly disclosed in the independent or dependent claims.

Present claims 1, 2,4-7 relate to a compound defined by reference to a desirable characteristic or property, namely prodrugs. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I) and their specific esters as defined on p. 13, l. 22-28 and l. 32-p. 14 l.7.

Present claim 8 refers to the compounds of examples 1-375. Such a way of formulating a claim does not comply with Rule 6.2(a) PCT. The search has been restricted to the compounds of the examples which fall within the scope of claim 1 (It should be noted that any other interpretation of this claim would lead to a lack of unity, as many of the examples are intermediates which lack the pyrimidine ring which is essential to the compounds of claim 1).

Claims 10-12 and 14-16 refer to methods of treatment using "compounds of the present invention". Many specific compounds and general formulae are disclosed in the present description, some of which are compounds of claim 1 and others are intermediates. It is not clear whether "compounds of the present invention" means compounds of claim 1 or all compounds disclosed in the description. The search has been performed assuming only

compounds of claim 1 are meant.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-26

   Compounds of formula (I), their pharmaceutical compositions, methods of use and processes of preparation.

2. Claim : 27

   Process for preparing compounds of formula (XV)